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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

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INVENTOR(S)

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☐ *Additional inventors are being named on the __ separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

Chiral 1,8-Diarylnaphthalenes, Methods of Making Them, and Their Use As Sensors

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☒ Applicant claims small entity status. See 37 CFR 1.27.

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Respectfully submitted,
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PROVISIONAL APPLICATION FOR PATENT

Chiral 1,8-Diarylnaphthalenes, Methods of Making Them, and Their Use as Sensors

Background of the Invention

Chemical sensors are highly useful in the chemical and pharmaceutical industry. Chemical sensors are used to determine the concentration of metal ions, such as calcium, and important gases, such as NO, O_2, and CO_2, in biological samples. For example, sensors are used to determine the level of calcium ions (Ca(II)) in the blood of animals. In addition, chemical sensors are important in the development of analytical techniques to measure the enantiomeric purity of chiral compounds. Analytical techniques to determine enantiomeric purity are important to the pharmaceutical industry because many biologically active compounds are single enantiomers.

In general, a chemical sensor consists of a receptor and a transducer. The receptor selectively binds the analyte while the transducer generates a signal based on the change in a chemical parameter that occurs in response to analyte binding. The sensitivity of the sensor is defined by the minimum amount of analyte that induces an identifiable signal relative to the noise. The selectivity of the sensor corresponds to its capacity to distinguish the analyte from the other chemical species which may be present in the medium. A very selective sensor is distinguished by the fact that the signal induced by the presence of the analyte is much more intense than the signal induced by any other chemical species present in the same amount. One of the main difficulties encountered in this field is to prepare sensors which are both sensitive and highly selective.

Recently there has been an increasing interest in the development of practical, sensitive and miniaturized probe systems for use in monitoring metal ions in biological media, living cells, and environmental samples. Fluorescence based sensors are especially useful due to their sensitivity, achieving attomole (10^{-8} mole) detection limits. Such sensors often use probes that have chemical reagents or bioreceptors (such as an antibody) chemically bound to optical fibers or physically entrapped in sensing microcavities containing liquid reagents or gels attached to the

distal end or to the cladding of the optical fiber. Direct attachment allows fast response time since sensor response depends on the mass transfer rate of the analyte to the immobilized reagent. In some cases, gels may be saturated with large quantities of reagent in order to enhance the sensitivity of the sensor. Physical entrapment onto the probe can also be another form of immobilization that is suitable to chemical or biological reagents. Immobilization on cellulose or poly(vinyl chloride) films allows greater loading, but decreases response time because the reagent is immobilized in single layers.

Several chemical sensors have been developed for the detection of metal ions. One of the first fluorescent calcium indicators was 2-{[2-[bis(carboxymethyl)amino]-5'-methylphenoxy]methyl}-6-methoxy-8-[bis(carboxymethyl)amino]quinoline (Quin-2). See R. Y. Tsien *Biochemistry* **1980**, *19*, 2396. Calcium binding to this sensor elicits an increase of fluorescence intensity of this compound. In comparison, Mauze et al. describe a chemical sensor comprising 2,2-bis(3,4-(15-crown-5)-2-nitrophenylcarbamoxymethyl)tetradecanol-14 which has at least one binding site and is provided with a fluorophore such as Rhodamine-B at that binding site. See U.S. Pat. 5,154,890. The sensing material is immobilized in a gel of polyacrylamide. U.S. Pat. No. 5,176,882 teaches a dual fiberoptic cell for multiple serum measurements where both a gas and an ion are analyzed simultaneously using a single probe having two separate fiber optic sensors incorporated therein. The gas is detected by the color change of a dye and the ion is detected by the fluorescing of a fluorescent metal ion sensitive dye. Nevertheless, sensors which have been developed to this point have several deficiencies, including low sensitivity due to weak analytical signal, low selectivity due to interferences, long term instability because of degradation of the immobilized reagent or its desorptive loss from the support, and/or slow response time because of barriers to mass transport in the polymer support.

Analytical methods to measure enantiomeric purity are needed because many biologically active compounds, such as pharmaceuticals, agrochemicals, flavors, and nutrients, are chiral. In fact, more than 50% of today's top-selling drugs are single enantiomers. The increasing demand for enantiopure chemicals has been accompanied by significant progress in asymmetric synthesis and catalysis. See (a) Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E. (Eds.) "Stereoselective Synthesis" in "Methods of Organic Chemistry", Houben-Weyl, Vol. 21a-21f, 4th edition., Thieme, Stuttgart, 1995; (b) Gawley, R. E. Aubé, J. "Principles of Asymmetric Synthesis" Tetrahedron Organic Chemistry Series, Elsevier, New York, 1996; (c) Ho, T.-L.

"Stereoselectivity in Synthesis" Wiley-VCH, New York, 1999; (d) Jonathan, M. J. W. "Catalysis in Asymmetric Synthesis" Sheffield Academic Press, Sheffield, 1999; and (e) Ojima, I.; (Ed.) "Catalytic Asymmetric Synthesis" 2nd edition, Wiley-VCH, New York, 2000. In addition, many analytical techniques, such as chiroptical methods, NMR spectroscopy, mass spectrometry, electrophoresis, and chromatography using chiral stationary phases, have been developed for the determination of the enantiomeric purity of chiral compounds. See Eliel, E. L.; Wilen, S. H. "Stereochemistry of Organic Compounds" John Wiley and Sons, New York, 1994, pp. 214-274.

Stereoselective analysis is very important to verify the purity and stereochemical stability of chiral chemicals and drugs. It also plays an integral part in the development of new asymmetric reactions. Recently, high-throughput screening (HTS) methods based on chiral chromatography for fast evaluation of enantioselective catalysts have been developed. See Wolf, C.; Hawes, P. A. *J. Org. Chem.* **2002**, *67*, 2727-2729; Wolf, C.; Francis, C. J.; Hawes, P. A.; Shah, M. *Tetrahedron: Asymm.* **2002**, *13*, 1733-1741; and Duursma, A.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2002**, *58*, 5773-5778. It has been demonstrated that multi-substrate screening followed by chromatography can provide yields, stereoselectivity, catalytic activity, chiral induction, and substrate tolerance of a catalyst in a single experiment. However, employing chromatography in HTS is usually too time-consuming, i.e. individual substrate screening combined with real-time enantioselective analysis seems to be a more promising approach.

Routine analysis of the enantiomeric composition of a sample usually entails chiral chromatography using expensive GC or HPLC columns, chiroptical methods, electrophoresis with chiral additives or NMR spectroscopy with chiral shift reagents. Enantioselective sensing based on fluorescence spectroscopy offers a variety of advantages over these techniques including different detection modes (fluorescence quenching, enhancement, and lifetime), high sensitivity, low cost of instrumentation, waste reduction, time efficiency, and the possibility of performing real-time analysis. Because of the high sensitivity inherent to fluorescence spectroscopy only a very small amount of the sensor is required, which makes this technique more cost-effective and practicable than chromatography. To date, only a few enantioselective fluorescence sensors including chiral macrocycles, dendrimers, or oligomers have been reported. See Lin, J.; Hu, Q.-S.; Xu, M.-H.; Pu, L. *J. Am. Chem. Soc.* **2002**, *124*, 2088-2089; Lee, S. J.; Lin, W. *J. Am. Chem. Soc.* **2002**, *124*, 4554-4555; Xu, M.-H.; Lin, J.; Hu, Q.-S.; Pu, L. *J. Am.*

Chem. Soc. **2002**, *124*, 14239-14246; and Ma, L.; White, P. S.; Lin, W. *J. Org. Chem.* **2002**, *67*, 7577-7586.

Enantioselectivity in energy transfer reactions between a variety of chiral quencher molecules and photoexcited chiral Lanthanide chelates has also been observed by time-resolved or steady-state circularly polarized luminescence measurements. See Meskers, S. C. J.; Dekkers, H. P. J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6413-6414 and Meskers, S. C. J.; Dekkers, P. J. M. *J. Phys. Chem. A* **2001**, *105*, 4589-4599. Nevertheless, the development of enantioselective sensing to a broadly applicable technique requires the design of new selector molecules combining well-defined stereoselective recognition of various classes of compounds with the advantage of fluorescence detection.

Summary of the Invention

One aspect of the invention relates to 1,8-diarylnaphthalene compounds. In certain embodiments, the aryl group is an optionally substituted acridyl group. In a preferred embodiment, the acridyl group is substituted with a methyl, isopropyl, or 3,5-methylphenyl group. In a preferred embodiment, the compound of the invention is a single diastereomer. In certain embodiments, the compounds of the invention relate to the *N*-oxide of a 1,8-diacridylnaphthalene. In a preferred embodiment, the acridyl group is substituted with 3,5-methylphenyl group. In a preferred embodiment, the *N*-oxide compound of the invention is a single enantiomer.

Another aspect of the present invention relates to a method of detecting the presence of an analyte by monitoring the fluorescence of the compound of the invention in the presence of the analyte. In certain embodiments, the analyte is a metal ion. In a preferred embodiment, the analyte is Cu^{2+}.

Another aspect of the present invention relates to a method of determining the enantiomeric purity of an analyte by monitoring the fluorescence of the compound of the invention in the presence of the analyte. In certain embodiments, the analyte is a compound that is capable of hydrogen bonding. In a preferred embodiment, the analyte is a compound containing a hydroxyl, carboxylic acid, or amine functional group.

Brief Description of Figures

Figure 1 depicts the structure of 1 exhibiting antiparallel (*anti*-isomer) or parallel (*syn*-isomer) 2-methylphenyl moieties.

Figure 2 depicts the synthesis of 1,8-diacridylnaphthalenes **2** and **3**.

Figure 3 depicts Stille cross-coupling products obtained from stannane **12** and 1,8-dihalonaphthalenes.

Figure 4 depicts optimized results of the Pd-catalyzed cross-coupling reactions ([a]DMF, 140 °C, 18 h; [b]DMF, 100 °C, 18 h [c]DMF, 140 °C, 5 h).

Figure 5 depicts possible transmetallation pathways during the second catalytic cycle of the Pd-catalyzed Stille coupling of 1-(4-isopropyl-9-acridyl)-8-bromonaphthalene, **16**, and stannane **12**.

Figure 6 depicts a space filling model of *anti*-**2** calculated by PM3.

Figure 7 depicts a PM3 Computation of the ground state of *anti*- (left) and *syn*-**3** (right).

Figure 8 depicts fluorescence quenching of *syn*-**2** using various concentrations of CuCl. Diacridylnaphthalene *syn*-**2** was dissolved in acetonitrile at a concentration of 10^{-6} M.

Figure 9 depicts fluorescence quenching of *syn*-**2** using various concentrations of $CuCl_2$. Diacridylnaphthalene *syn*-**2** was dissolved in acetonitrile at a concentration of 10^{-6} M.

Figure 10 depicts Stern-Völmer plot of *syn*-**2** in the presence of Cu(I) and Cu(II) chloride. The concentration of *syn*-**2** was 10^{-6} M.

Figure 11 depicts Stern-Völmer plot of *syn*-**2** in the presence of Cu(II) and Zn(II) chloride. The concentration of *syn*-**2** was 10^{-6} M.

Figure 12 depicts UV Titration of *syn*-**2** with $CuCl_2$. Inset: Job plot recorded at 225 nm. Sum of concentrations was fixed at 1.5×10^{-5} M.

Figure 13 depicts UV Titration of *anti*-**2** with $CuCl_2$. Inset: Job plot recorded at 225nm. Sum of concentrations was fixed at 1.5×10^{-5} M.

Figure 14 depicts counterion effect on the fluorescence quenching of *syn*-**2** in acetonitrile. The concentration of *syn*-**2** was 5 x 10^{-6} M.

Figure 15 depicts ^{1}H-NMR of the methyl signals of the *anti*- and *syn*-isomers of 1,8-bis(9,9'-dimethyl-4,4'-diacridyl)naphthalene, **2**, in absence (left) and in presence (right) of 1.2 mol equivalents of (+)-Eu(tfc)$_3$.

Figure 16 depicts the determination of the extinction coefficient, ε, of **2** in CH_2Cl_2.

Figure 17 depicts the determination of the extinction coefficient, ε, of **3** in CH_2Cl_2.

Figure 18 depicts a fluorescence spectrum of a 4.6:1 *anti/syn* mixture of **2** in benzene and dichloromethane.

Figure 19 depicts a fluorescence spectrum of *anti*-**2** (left) and *syn*-**2** (right) in benzene.

Figure 20 depicts a fluorescence spectrum of **3** in benzene and dichloromethane.

Figure 21 depicts the structures of atropisomers **18-21**.

Figure 22 depicts the isomerization of **18**.

Figure 23 depicts a PM3-calculated ground state of (*R,R*)-**22**.

Figure 24 depicts the synthesis of 1,8-diacridylnaphthalene *N,N'*-dioxide **33**.

Figure 25 depicts a CD spectrum of the enantiomers of **33**.

Figure 26 depicts a side view (top) and view along the naphthalene plane (bottom) of the X-ray structure of **33** (closed structure). Co-crystallizing dichloromethane is omitted for clarity.

Figure 27 depicts a side view (top) and view along the naphthalene plane (bottom) of the X-ray structure of **33**-H_2O (open structure). Co-crystallizing acetonitrile is omitted for clarity.

Figure 28 depicts crystal data and structure refinement for single crystals of *N,N'*-dioxide **16**.

Figure 29 depicts a stern-Völmer plot of enantiopure **33** in the presence of (*R*)- and (*S*)-*N*-t-Boc-valine, **17**.

Figure 30 depicts a UV spectrum of *anti*-**33** in acetonitrile.

Figure 31 depicts a fluorescence spectrum of *anti*-**33** in acetonitrile.

Figure 32 depicts a Stern-Volmer plot for *syn*-**18** in presence of Cu^{2+} and Cu^{+} (Linear Stern-Volmer plots Selectivity factor ($Ksv(Cu^{2+})/Ksv(Cu^{+}) = 111$).

Figure 33 depicts a Stern-Volmer plot for *syn*-**18** in presence of Cu^{2+} and Zn^{2+} (Linear Stern-Volmer plots Selectivity factor ($Ksv(Cu^{2+})/K_{SV}(Zn^{2+}) = 72$).

Figure 34 depicts a Stern-Volmer plots for *syn*-**18** in presence of Zn^{2+}, Fe^{2+} and Fe^{3+}.

Figure 35 depicts a single crystal structure of *syn*-**19**. (Crystal system: Monoclinic, Space group: $P2_1/n$; Selected bond lengths (Å): C1-C2: 1.487, C4-C5: 1.499, N1-N2: 4.028, C7-C10: 3.865; Selected torsion angles: C3-C4-C5-C6: 101.3°, C1-C2-C4-C5: 21.8°).

Figure 36 depicts a single crystal structure of 2-(2'-Methylphenylamino)benzoic Acid **25** (Crystal system: Monoclinic Space group: $C2_1/c$; Selected bond lengths: (Å) C1-O1: 1.238, C1-O2: 1.323, C3-N1: 1.369, C5-N1: 1.414; Torsion angle: C2-C3-C4-C5: 134.1°).

Figure 37 depicts a single crystal structure of 2-(2'-Isopropylphenylamino)benzoic Acid **24** (Crystal system: Triclinic, Space group: P-1; Select bond lengths (Å): C1-O1: 1.236, C1-O2: 1.324, C3-N1: 1.371, C5-N1: 1.417; Torsion angle: C2-C3-C4-C5: 81.4°).

Detailed Description of the Invention

Background and Design of 1,8-Diarylnaphthalene Sensors

The unique stereochemical, electronic, and photochemical properties of sterically congested aromatic compounds have attracted considerable attention during recent years because they afford promising optoelectronic devices, rotors, and chemical sensors. See Wong, K.-T.; Chien, Y.-Y.; Chen, R.-T.; Wang, C.-F.; Lin, Y.-T.; Chiang, H.-H.; Hsieh, P.-Y.; Wu, C.-C.; Chou, C. H.; Su, Y. O.; Lee, G.-H.; Peng, S.-M. *J. Am. Chem. Soc.* **2002**, *124*, 11576-11577 and Rathore, R.; Deselnicu, M. I.; Burns, C. L. *J. Am. Chem. Soc.* **2002**, *124*, 14832-14833. The preparation of conformationally stable 1,8-diarylnaphthalenes has been an unresolved challenge since Clough and Roberts reported the synthesis of atropisomeric 1,8-bis(2,2'-dimethyl-1,1'-diphenyl)naphthalene, **1**, almost 30 years ago, Figure 1. Clough, R. L.; Roberts, J. D. *J. Am. Chem. Soc.* **1976**, *98*, 1018-1020. Exhibiting an energy barrier to isomerization of 100 kJ/mol, **1** remains the most stable atropisomer of this class of compounds reported to date.

Despite the variety of cross-coupling procedures that has been developed for the synthesis of biaryls in recent years, coupling reactions using highly hindered aromatic compounds has rarely been achieved. Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L *J. Am. Chem. Soc.* **2002**, *124*, 1162-1163 and references therein. A number of aryl and hetaryl groups have been introduced into the *peri*-positions of naphthalene by us and others to study the energy barrier to rotation about the naphthyl-aryl bond. Incorporation of *ortho*- or *meta*-substituted aryl moieties into both *peri*-positions of naphthalene results in two chiral *anti*-isomers and one meso *syn*-isomer. See (a) Cozzi, F.; Ponzini, F.; Annunziata, R.; Cinquini, M.; Siegel, J. S. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1019-1020; (b) Ernst, L.; Sakhaii, P. *Magn. Reson. Chem.* **2000**, *38*, 559-565; (c) Wolf, C.; Ghebremariam, B. T. *Tetrahedron: Asymm.* **2002**, *13*, 1153-1156; and (d) Wolf, C.; Tumambac, G. E. *J. Phys. Chem. A* **2003**, *107*, 815-817.

Computational studies and x-ray analysis have shown that the *peri*-aryl rings are coplanar and almost perpendicular to the naphthalene moiety in the ground state. In contrast to the significant steric hindrance to isomerization suggested by CPK models, 1,8-diarylnaphthalenes such as **1** are not stable to interconversion at room temperature. The development of a synthetic route toward conformationally stable, atropisomeric 1,8-diarylnaphthalenes would facilitate studies of intramolecular interactions between stacked aryl groups and has been considered an entry to a new class of chiral ligands for asymmetric catalysis. See Sinnokrot, M. O.; Valeev, E. F.; Sherrill, C. D. *J. Am. Chem. Soc.* **2002**, *124*, 10887-10893 and Steele, M.; Watkinson, M.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 588-598.

To date, all attempts to prepare 1,8-diarylnaphthalenes exhibiting conformational stability have been unsuccessful because of the severe steric repulsion that one can expect during the construction of such a highly constrained framework. Based on *ab initio* calculations, Thirsk et al. recently predicted a rotational energy barrier of approximately 160 kJ/mol to isomerization for *ortho*-substituted 2,7-diisopropoxy-1,8-diarylnaphthalenes. However, their attempts to synthesize such conformationally stable atropisomers using Suzuki cross-coupling were not successful. Thirsk, C.; Hawkes, G. E.; Kroemer, R. T.; Liedl, K. R.; Loertig, T.; Nasser, R.; Pritchard, R. G.; Steele, M.; Warren, J. E.; Whiting, A. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1510-1519.

We assumed that introduction of acridyl moieties into the *peri*-positions of naphthalene would result in a rigid scaffold that renders rotation of the aryl rings about the acridyl-naphthalene axis impossible. Careful incorporation of substitutents into the fluorescent acridyl rings was expected to afford bidentate selectors exhibiting well-defined pockets for coordination to Lewis or Bronsted acids. Selective interactions between this new class of chemosensors and metal ions or other substrates would be measurable by sensitive fluorescence spectroscopy and allow real-time monitoring of trace analytes. Although a variety of fluorescent sensors for alkali, alkaline earth, and transition metals have been developed, high ion selectivity and the ability to differentiate between different oxidation states remain a challenge. See Zheng, Y.; Gattas-Asfura, K. M.; Li, C.; Andreopoulos, F. M.; Pham, S. M.; Leblanc, R. M. *J. Phys. Chem. B* **2003**, *107*, 483-488 and Kim, J. S.; Noh, K. H.; Lee, S. H.; Kim, S. K.; Kim, S. K.; Yoon, J. *J. Org. Chem.* **2003**, *68*, 597-600.

The present invention generally relates to molecules that may be used as sensors to detect chiral compounds, metal ions, or biopolymers such as RNA or DNA. In certain embodiments, the compounds of the invention may be useful as Lewis acidic or Lewis basic catalysts. We have discovered the first synthetic route to 1,8-dihetarylnaphthalenes exhibiting conformational stability, i.e., hindered rotation about the hetaryl-naphthalene bond at high temperature. We obtained, purified and separated all possible isomers, i.e., the meso-syn isomer as well as enantiopure anti-isomers. We have discovered selector molecules that can differentiate between enantiomers of a broad range of classes of chiral compounds, including but not limited to amines amino acids and alcohols. The 1,8-diacridylnaphthalenes also show selectivity for various metal ions. We have discovered that 1,8-diacridylnaphthalenes may be used for the analysis of small amounts of metal ions and chiral compounds using fluorescence or NMR spectroscopy. 1,8-Remarkably, 1,8-diacridylnaphthalenes are also useful in asymmetric catalysis, determination of the absolute configuration of a stereogenic center in a compound, and selective interactions with RNA or DNA sequences.

Synthesis of 1,8-Diarylnaphthalenes

The synthesis of 1,8-diarylnaphthalenes is depicted in Figure 2. Retrosynthetic analysis of 1,8-bis(4,4'-dimethyl-9,9'-diacridyl)naphthalene (**2**) and 1,8-bis(4,4'-diisopropyl-9,9'-

diacridyl)naphthalene (**3**) suggested Stille or Suzuki cross-coupling of 1,8-dibromo- or 1,8-diiodonaphthalene with a 4-substituted-9-acridyl stannane or boronic acid derivative, which can be formed via ring construction from 2-substituted anilines. We have found that 1,8-bis(4,4'-dialkyl-9,9'-diacridyl)naphthalenes **2** and **3** can be synthesized from readily available 2-chlorobenzoic acid, **4**, and anilines **5** and **6**, respectively.

Commercially available acid, **4**, was converted to 4-alkyl-9-trimethylstannylacridine, **11** and **12**, in 3 steps with high overall yield. First, we attempted Stille cross-coupling of stannane **12** and 1,8-diiodonaphthalene using $Pd(PPh_3)_4$ as the catalysts. However, **14** and **15** were obtained as the only cross-coupling products in addition to degradation products of stannane **11**, Figure 3. The structure of **14** and **15** was determined by NMR and LC/APCI/MS.

We therefore decided to use 1,8-dibromonaphthalene in the Stille reaction. See Seyferth, D.; Vick, S. C. *J. Organomet. Chem.* **1977**, 141, 178-187. Screening of various catalysts such as $Pd(PPh_3)_4$, $PdCl_2$dppf or $Pd_2(dba)_3$/t-Bu_3P and optimization of reaction conditions revealed that employing $Pd(PPh_3)_4$ and CuO in DMF at 140 °C affords 1,8-bis(4,4'-dialkyl-9,9'-diacridyl)naphthalenes **2** and **3** via Stille coupling of stannanes **11** or **12** with 1,8-dibromonaphthalene in remarkable yields. We were pleased to find less than 10 % of coupling by-products **13**, **14** and **15** under these conditions, Figure 4. Notably, Suzuki coupling of 1,8-dibromonaphthalene and 4-isopropoyl-9-acridylboronic acid or its pinacolate derivative employing $Pd(PPh_3)_4$, $PdCl_2$dppf or $Pd_2(dba)_3$/t-Bu_3P as the catalyst as well as *t*-BuOK, K_3PO_4 or Cs_2CO_3 as the base in DME and DMF, respectively, did not result in the formation of the desired coupling product.

The observed cross-coupling by-products are indicative of the steric hindrance that occurs during the Pd-catalyzed reaction between the intermediate 1-(4-isopropyl-9-acridyl)-8-bromonaphthalene, **16**, and another stannane **12**, Figure 5. Oxidative addition of **16** to the Pd catalysts provides a reactive Pd complex **17** that can undergo transmetallation followed by reductive elimination to yield Stille products **3** and **13** or intramolecular coupling through Pd-activation of a *peri* acridyl C-H bond to form **14** and **15**. The formation of carbon-carbon bonds via metal-mediated C-H bond activation has been reported by others and used as a powerful strategy for the synthesis of complex compounds. See (a) Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 103-105; (b) Reetz; M. T.; Wanninger, K.; Hermes, M. *J. Chem. Soc. Chem.*

Commun. **1997**, 535-536; (c) Jia, C.; Kitamura, T.; Fujiwara, Y.; *Acc. Chem. Res.* **2001**, *34*, 633-639;(d) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731-1769; and (e) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856-11857.

Due to the steric hindrance that can be expected between Pd complex **17** and a second stannyl reagent **12**, the transfer of a methyl group instead of the acridyl moiety becomes a competitive side reaction that results in the formation of the undesired coupling product **13**. Since the transmetallation between **17** and **12** is considered to be slow, C-H insertion of **17** and subsequent reductive elimination affords **14** and **15**.

Because of the severe steric hindrance and possible side reactions inherent to their synthesis, highly constrained 1,8-diarylnaphthalenes exhibiting conformational stability have not been reported previously. The preparation of **2** and **3** in 25% yield using our CuO-promoted Stille coupling procedure is quite remarkable since it affords two consecutive coupling steps.

We were pleased to find that the diastereoisomers of **2** and **3** can be separated by HPLC on a (*S*)-Phenylglycine column. Semi-preparative separation allowed us to determine the *anti/syn* ratio of **2** and **3** as 4.6:1 and 1:1, respectively. The isomer ratios of **2** and **3** determined after semi-preparative HPLC separation are in very good agreement with ^{1}H-NMR integration results of the product mixtures. The *syn* and *anti*-conformation of **2** was determined by ^{1}H-NMR using a chiral Lanthanide shift reagent. The formation of diastereomeric complexes of the C_2-symmetric *anti*-isomers of **2** exhibiting anisochronous signals was observed in the presence of (+)-Eu(tfc)$_3$, whereas the signals of the methyl protons of the *meso*-form are downfield-shifted but are still isochronous, see Figure 15. Addition of of (+)-Eu(tfc)$_3$ to a solution of the *syn*- and *anti*-isomers of **2** causes a significant downfield shift for the meso *syn*-isomer compared to the chiral *anti*-isomers. The chiral lanthanide shift reagent also differentiates between the two enantiomers of *anti*-**2** which proves that the major fraction obtained by Stille coupling of 1,8-dibromonaphthalene and **12** is *anti*-**2**. The conformation of the two isomers of **3** could not be determined using NMR shift reagents or NOESY experiments. In addition, we were not able to separate the enantiomers of *anti*-**2** and *anti*-**3**, respectively.

Isomerization via rotation of one acridyl ring about the chiral acridyl-naphthyl axis is highly restricted due to steric hindrance. According to PM3 calculations, diacridyls **2** and **3** afford compact structures in which both acridyl rings are roughly perpendicular to the mean

plane of the naphthyl ring with dihedral angles ranging from 85° to 95°. The acridyl moieties are slightly twisted away from each other and undergo enforced π-stacking, Figure 6. See (a) Hunter, C. A.; Lawson, K. R.; Perkins, J.; Urch, C. J. *J. Chem. Soc., Perkin Trans. 2* **2002**, 651-669 and Rashkin, M. J.; Waters, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 1860-1861.

The isolated isomers were heated in acetonitrile in a closed vessel to 180 °C for 24 h. As expected, rotation of either acridyl moiety about the chiral acridyl-naphthalene axis of **2** and **3** is highly sterically hindered and HPLC analysis did not show any sign of isomerization. Utilizing reversible first-order kinetics and the Eyring equation, the Gibbs standard activation energy, $\Delta G^{0\neq}$, for the isomerization of **2** and **3** was calculated to be higher than 180 kJ/mol. Notably, acridylnaphthalens **2** and **3** began to decompose at 200 °C.

Investigation of the photochemical properties of **2** and **3** revealed UV absorption maxima at 246 nm (log ε = 8.02 and 8.06, respectively). The UV spectra proved to be reminiscent of isolated, non-conjugated naphthyl and acridyl chromophores as one would expect for a structure exhibiting both hetaryl rings perpendicular to the naphthalene plane. The UV data are thus in agreement with the results of our PM3 calculations. The fluorescence spectra of **2** and **3** were found to be significantly red-shifted compared to that of acridine which exhibits an emission maximum around 400 nm in benzene. This may be attributed to the enhanced π-stacking of the two acridyl rings. Fluorescence studies of both isomers of diacridine **3** revealed only one maximum at approximately 530 nm and a quantum yield of 18%. In contrast, the fluorescence of the isomers of **2** proved to be significantly different. We found that *syn*-**2** is a blue light emitter with a fluorescence maximum at 460 nm, whereas excited *anti*-**2** emits green light at approximately 540 nm. Notably, *syn*-**2** was found to be more fluorescent than its diastereoisomeric *anti*-isomer. The quantum yields for *syn*- and *anti*-**2** were determined as 22% and 13%, respectively. The striking difference in the flourescence behavior of the isomers of **2** may be attributed to increased π-π interactions between the *anti*-parallel acridyl rings of *anti*-**2**. The distance between the acridyl nitrogens of *syn*-**2** was determined as 3.6 Å based on PM3 optimization of the ground state. By contrast, PM3 calculations suggest a N-N distance of only 3.4 Å for *anti*-**2**. We assume that the close proximity of the acridyl rings facilitates non-radiative relaxation of excited *anti*-**2** resulting in a significantly lower quantum yield than its *syn*-isomer. Computational studies of the ground state of *syn*- and *anti*-**3** provided N-N distance of 3.8 Å for

both isomers, which explains their indistinguishable fluorescence maximum and quantum yield, Figure 7.

In summary, we have synthesized conformationally stable 1,8-diarylnaphthalenes via CuO-promoted Stille cross-coupling of 1,8-dibromonaphthalene and 4-alkyl-9-trimethylstannylacridines. The *syn*- and *anti*-isomers of 1,8-bis(4,4'-dimethyl-9,9'-diacridyl)naphthalene, **2**, and its diisopropyl analog **3** have been isolated for investigation of their stereodynamic properties. No sign of *syn/anti*-isomerization was observed even at high temperatures indicating a rotational energy barrier above 180 kJ/mol.

Use of 1,8-Diarylnaphthalenes as Sensors

We chose to investigate the usefulness of this new class of conformationally stable, bidentate 1,8-dihetarylnaphthalenes combining unique stereochemical and photoluminescent features as selective sensors. The majority of fluorosensors developed to date are macrocyclic structures exhibiting a chelating group and a fluorophore physically separated by a spacer. See de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem Rev.* **1997**, *97*, 1515-1566. However, small sensors afford advantageous cell permeability properties and are therefore particularly promising for biomedical trace analysis.

Because of its higher quantum yield, we decided to employ the *syn*-isomer of **2** in metal ion-sensing studies. Fluorescence emission titrations with *syn*-**2** and CuCl and $CuCl_2$ were performed in acetonitrile at room temperature. We did not observe any significant red or blue shifts in the emission spectra of *syn*-**2** in presence of the metal ions. Addition of CuCl did not result in significant quenching even at high excess, Figure 8. By contrast, titration of the same sensor with $CuCl_2$ revealed highly efficient quenching, Figure 9.

Because of its considerably different fluorescence response to Cu(I) and Cu(II) ions, the *syn*-isomer of **2** may be used as a highly selective sensor for real-time qualitative and quantitative analysis of the oxidation state of copper ions in solution. Binding to a metal ion opens new vibrational or electronic pathways for non-radiative relaxation of excited *syn*-**2**. Coordination of the diacridylnaphthalene sensor to Cu(II) exhibiting a d^9-electronic

configuration is likely to result in considerable fluorescence quenching because of photo-induced electron transfer.

Interestingly, we observed non-linear Stern-Völmer quenching of *syn*-**2** by Cu(II) chloride. A fluorescence titration experiment with $CuCl_2$ gave a sigmoidal quenching curve indicating cooperative recognition such as formation of less fluorescent agglomerates at high Cu(II)/sensor ratio, Figure 10. Chemical sensing based on cooperative recognition has rarely been observed and is believed to result in higher selectivity compared to non-cooperative sensing exhibiting a linear fluorescence response. See Glass, T. E. *J. Am. Chem. Soc.* **2000**, *122*, 4522-4523.

By contrast, photo-induced electron transfer is not significant in Cu(I)-*syn*-**2** because of the d^{10}-electronic configuration of the metal ion. Further titration experiments revealed that the selector is also capable of differentiating between $CuCl_2$ and $ZnCl_2$. Stern-Völmer plots of the two salts show that Zn(II) barely induces fluorescence quenching of *syn*-**2**, Figure 11. This may also be attributed to negligible photo-induced electron transfer of excited Zn(II)-*syn*-**2**.

We conducted UV titration experiments of *syn*- and *anti*-**2** using Cu(II) chloride for the determination of the stoichiometry of the metal-sensor complexes formed in acetonitrile, Figures 12 and 13. In accordance with our fluorescence experiments, we did not observe any significant red or blue shifts in the absorption spectra of the diacridylnaphthalenes in presence of Cu(II). Job analysis of Cu(II) chloride and *syn*-**2** or *anti*-**2** at a total concentration of 1.5×10^{-5} M revealed the existence of one maximum at a molar ratio of 0.5 which is in agreement with the formation of an equimolar complex, Figures 12 and 13. See Connors, K. A. *Binding Constants, The Measurement of Molecular Complex Stability*; Wiley: New York, 1987. Notably, a job plot affords the sensor/metal ratio but does not differentiate between 1:1, 2:2 complexation or formation of even higher aggregrates, which would explain the cooperative recognition of Cu(II) observed with *syn*-**2**.

The selectivity between copper and zinc ions is quite important for bioanalytical and environmental studies. Cu(II) and Zn(II) are essential trace elements that occur in metalloproteins with various biological functions in bacteria, plants and mammals. Cu(II) is also a significant environmental pollutant. An important requirement for an useful cation-selective sensor is the absence of a significant fluorescence response to anions also present in solution. We

therefore selected three different Cu(I) salts for fluorescence titration experiments to determine any counteranion effects on the photochemical properties of the sensor. Indeed, *syn*-**2** did not show any significant fluorescence quenching due to the presence of chloride, bromide or tetrafluoroborate, Figure 14. The Stern-Völmer plots obtained with CuCl and CuBr are almost superimposable, whereas quenching by $Cu(ACN)_4BF_4$ was found to be approximately 7% more effective.

In summary, fluorescence titration experiments with the *syn*-isomer of **2** revealed highly efficient quenching by Cu(II) ions, which was attributed to cooperative recognition. Job analysis based on UV titration experiments revealed formation of a complex exhibiting equimolar amounts of the sensor and Cu(II). Almost no quenching effects were observed with Cu(I) and Zn(II) salts, which is probably a consequence of negligible photo-induced electron transfer pathways for non-radiative relaxation. The fluorescence quenching was found to be cation-selective and almost independent of counteranions present in solution. The high sensitivity inherent to fluorescence spectroscopy combined with the remarkable ion-selectivity of this new class of chemosensors opens new venues for probing small traces of metal ions.

We believe that the development of a synthetic route toward C_2-symmetric and conformationally stable 1,8-diarylnaphthalenes such as *anti*-**2** and *anti*-**3** will allow the exploration of a new class of compounds for enantioselective sensing of chiral molecules. The synthesis and enantioseparation of new axially chiral 1,8-dihetarylnaphthalenes that are capable of participating in diastereomeric interactions that can be quantitatively measured by fluorescence quenching are contemplated embodiments of the present invention.

Design of 1,8-Diarylnaphthalene N-Oxide Sensors

In continuation of our studies of the stereodynamics of axially chiral 1,8-dipyridylnaphthalenes 1-4, we have envisioned the development of a new class of compounds derived from the 1,8-dihetarylnaphthalene framework for stereoselective sensing, Figure 21. See Wolf, C.; Ghebremariam, B. T. *Synthesis* 2002, 749-752; Wolf, C.; Ghebremariam, B. T. *Tetrahedron: Asymm.* 2002, 13, 1153-1156; and Wolf, C.; Tumambac, G. E. *J. Phys. Chem. A* 2003, *107*, 815-817. 1,8-Disubstituted naphthalenes display striking properties because of their unique geometry and related atropisomerism. A variety of *peri* substituted naphthalene

derivatives exhibiting alkyl, aryl, and hetaryl groups has been synthesized to study steric and electronic interactions between π-stacked aryl rings. See Fields, D. L.; Regan, T. H. *J. Org. Chem.* **1971**, *36*, 2995-3001; Steele, M.; Watkinson, M.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 588-598. (k) Thirsk, C.; Hawkes, G. E.; Kroemer, R. T.; Liedl, K. R.; Loertig, T.; Nasser, R.; Pritchard, R. G.; Steele, M.; Warren, J. E.; Whiting, A. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1510-1519; Zoltewicz, J. A.; Maier, N. M.; Lavieri, S.; Ghiviriga, I.; Abboud, K. A. *Tetrahedron* **1997**, *53*, 5379-5388; and references therein. Both *peri* aryl rings have been reported to be cofacial and almost perpendicular to the naphthalene moiety in the ground state. The naphthalene moiety is twisted and the two aryl groups are splayed out to minimize steric interactions and through-space Coulomb repulsion between the *peri* substituents. Rotation about the pyridyl-naphthalene bond of 1,8-bis(2,2'-dimethyl-4,4'-dipyridyl)naphthalene, **1**, causes interconversion of the chiral *anti*-isomers to the meso *syn*-isomer via a T-shaped transition state exhibiting the edge of the rotating aromatic ring directed towards the face of the neighboring ring, Figure 22.

We determined the range of the Gibbs activation energy, $\Delta G^{\ddagger}$, for the *syn/anti*-diastereoisomerization of 1-4 as 64 to 73 kJ/mol using variable-temperature NMR spectroscopy (DNMR) and dynamic HPLC and computer simulation (DHPLC). See Gafni, A. *J. Am. Chem. Soc.* **1980**, *102*, 7367-7368 and Yorozu, T.; Hayashi, K; Irie, M. *J. Am. Chem. Soc.* **1981**, *103*, 5480-5484. We concluded that incorporation of two selectively substituted acridyl groups into the peri positions of naphthalene should result in conformationally stable, bidentate 1,8-bis(9,9'-diacridyl)naphthalenes that would be highly useful enantioselective sensors. See De Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515-1586.

Optimization of the ground state of (*R,R*)-1,8-bis(3,3'-di*iso*propyl-9,9'-diacridyl)naphthalene *N,N'*-dioxide, (*R,R*)-5, by PM3 calculations show that both acridine rings are cofacial and almost perpendicular to the naphthalene moiety, Figure 23. The distance between both oxygen atoms of **5** was calculated as 4.1 Å, which would provide an attractive coordination environment for organic molecules such as bidentate amines, alcohols, and carboxylic acids. Notably, chiral *N*-oxides have been employed as Lewis base or Lewis acid catalysts in various asymmetric reactions, including Michael additions, cyanosilylations, aldol

additions, and ring openings of meso epoxides. See Malkov, A. V.; Bell, M.; Vassieu, M.; Bugatti, V.; Kocovsky, P. *J. Mol. Catal.* **2003**, *196*, 179-186; Saito, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron* **2000**, *56*, 9589-9594; Chen, F. Feng, X.; Qin, B.; Zhang, G.; Jiang, Y. *Org. Lett.* **2003**, *5*, 949-952; Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233-4235; Tao, B.; and Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 353-354.

Because of the well-known usefulness of *N,N'*-dioxides in asymmetric catalysis and their ability to form strong complexes with hydrogen bond donors and a variety of metal ions, we concluded that axially chiral *N,N'*-dioxides such as **5** provide an attractive opportunity for developing new molecular sensors. See Karayannis, N. M.; Pytlewski, L. L.; Mikulski, C. M. *Coord. Chem. Rev.* **1973**, *11*, 93-159 and Ryzhakov, A. V.; Nizhnik, Y. P.; Andreev, V. P. *Russ. J. Org. Chem.* **2000**, *36*, 884-886. The structure of this new class of C_2-symmetric *N,N'*-dioxides is designed to (a) embed interactions with chiral molecules into a highly stereoselective environment, and to (b) utilize fluorescence spectroscopy to monitor stereoselective recognition.

Various high-throughput screening (HTS) methods utilizing chromatography for the evaluation of chiral catalysts have been developed by us and others. See Wolf, C.; Hawes, P. A. *J. Org. Chem.* **2002**, *67*, 2727-2729; Wolf, C.; Francis, C. J.; Hawes, P. A.; Shah, M. *Tetrahedron: Asymm.* **2002**, *13*, 1733-1741; and Duursma, A.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2002**, *58*, 5773-5778. Employing diethylzinc in the enantioselective alkylation of aldehydes to chiral alcohols we have shown that multi-substrate screening can provide yields, enantioselectivity, substrate specificity, and sense of chiral induction of a catalyst. However, multi-substrate one-pot screening often suffers from interference between simultaneously run reactions and chromatograpic separation of several products obtained from one reaction mixture is often difficult and time-consuming.

We anticipate that *N,N'*-dioxide **33** and derivatives thereof will be highly useful for HTS of the enantiomeric composition and absolute configuration of many chiral compounds and thus provide a new tool for real-time analysis of asymmetric reactions. The introduction of enantioselective fluorescent sensors to HTS is expected to afford superior sensitivity, time-efficiency, and applicability over other rapid methods based on electrophoresis, NMR, HPLC/CD, MS or enzymatic techniques. See (a) Reetz, M. T.; Kuhling, K. M.; Deege, A.; Hinrichs, H.; Belder, D. *Angew. Chem. Int. Ed.* **2000**, *39*, 3891-3893; (b) Evans, M. A.; Morken,

J. P. *J. Am. Chem. Soc.* **2002**, *124*, 9020-9021; (c) Ding, K.; Ishii, A.; Mikami, K. *Angew. Chem. Int. Ed.* **1999**, *38*, 497-501; (d) Taji, H.; Watanabe, M.; Harada, N.; Naoki, H.; Ueda, Y. *Org. Lett.* **2002**, *4*, 2699-2702; (e) Reetz, M. T. *Angew. Chem. Int. Ed.* **2002**, *41*, 1335-1338.

A few achiral fluorosensors have been used for HTS of combinatorial libraries but only one example of enantioselective analysis utilizing chiral probes has been reported to date. See (a) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 4306–4307; (b) Stauffer, S. R.; Beare, N. A.; Stambuli, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4641-4642; (c) Korbel, G. A.; Lalic, G., Shair, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 361-362. Since our results show that *N,N'*-dioxides such as **16** can be used for enantioselective recognition of chiral hydrogen bond donors, this new class of fluorosensors will allow real-time screening of various asymmetric reactions, e.g. the synthesis of chiral alcohols from aldehydes mentioned above or the synthesis of amino acids and amino alcohols.

Synthesis of 1,8-Diarylnaphthalene N-Oxides

We were able to prepare 1,8-bis(4,4'-dimethyl-9,9'-diacridyl)naphthalene, **23**, and 1,8-bis(4,4'-dimethyl-9,9'-diacridyl)naphthalene, **24**, utilizing CuO-promoted Stille cross-couplings of 1,8-dibromonaphthalene and 4-alkyl-9-trimethylstannylacridines as described above. The isolated meso *syn*- and C_2-symmetric *anti*-isomers of **23** and **24** did not show any sign of isomerization after heating to 180 °C for 24 h indicating a Gibbs activation energy for interconversion, $\Delta G^{\neq}$, of at least 180 kJ/mol based on the Eyring equation. However, using a variety of chiral HPLC columns we were not able to separate the enantiomers of *anti*-**23** or *anti*-**24**. In addition, formation of the corresponding *N*-oxides was found to proceed with very low yields, which is probably a consequence of steric shielding of the acridyl nitrogens by the adjacent alkyl groups.

Optimization of the conformation of *anti*-**24** by PM3 calculations confirmed the shielding effect of the ipso-isopropyl groups. We concluded that better accessibility of the acridyl nitrogens is required in order to facilitate formation of *N*-oxides and HPLC enantioseparation. We therefore decided to incorporate 3,5-dimethylphenyl moieties into position 3 of the acridyl rings, Figure 25.

Suzuki coupling of commercially available 3-bromoaniline, **25**, and 3,5-dimethylboronic acid afforded 3-(3,5-dimethylphenyl)aniline, **26**, in high yields. Treatment of **26** with 2-chlorobenzoic acid, **27**, gave *N*-3-(3,5-dimethylphenyl)anthranilic acid, **28**, which was converted to 9-bromo-3-(3,5-dimethylphenyl)acridine, **29**, using phosphorous oxybromide. As expected, we observed that 9-bromo-1-(3,5-dimethylphenyl)acridine was formed as a major by-product during ring construction. Lithiation of **29** at –78 °C followed by stannylation with trimethylstannyl chloride resulted in the formation of 3-(3,5-dimethylphenyl)-9-trimethylstannylacridine, **30**, in high yields. Employing stannane **30** and 1,8-dibromonaphthalene, **31**, in a CuO-promoted Stille coupling previously developed in our laboratories yielded 1,8-bis(3,3'-(3,5-dimethylphenyl)-9,9'-diacridyl)naphthalene, **32**. Oxidation of **32** using *m*-chloroperoxybenzoic acid gave 1,8-bis(3,3'-(3,5-dimethylphenyl)-9,9'-diacridyl)naphthalene *N,N'*-dioxide, **33**.

We were pleased to find that the *anti*-isomers of **32** and **33** can be separated into enantiomers on a Chiralcel OJ and Chiralpak AD column, respectively. The CD spectra of the enantiomers of **33** are shown in Figure 25.

To elucidate the three-dimensional structure of *N,N'*-dioxide **33** and to provide an understanding of its coordination sphere and potential as an enantioselective sensor, we obtained single crystals for X-ray analysis. From a dichloromethane solution, we obtained a co-crystal with one molecule of dichloromethane through slow diffusion of diethyl ether at room temperature. In addition, slow solvent evaporation of a solution of **33** in acetonitrile resulted in formation of another single crystal suitable for X-ray diffraction, Figures 27 and 28. The crystallographic coordinates of the single crystals of **33** have been deposited with the Cambridge Crystallographic Data Centre; deposition numbers CCDC 218158 and CCDC 218159.

Accordingly, **33** can afford at least two different conformations in the solid state. The 'open structure' exhibits a wider cleft between the two 3,5-dimethylphenyl moieties, whereas the 'closed structure' affords a smaller cleft. The closest distance between the ortho hydrogens of the two 3,5-dimethylphenyl rings, i.e. H(21) and (H21') was determined as 5.28 Å and 12.09 Å, respectively. Notably, the distance between the two *N*-oxide groups remains the same in both structures, i.e. 4.32 Å or 4.30 Å. In the open structure, the acridyl rings are slightly splayed away from each other about 3.2° and the torsion angle between the acridyl rings was found to be 24.8°.

The closed structure exhibits the acridyl moieties splayed about 4.8° and a torsion angle of -20.9°, Figure 28. Interestingly, the closed structure co-crystallized with one molecule of dichloromethane (not shown) whereas the open structure co-crystallized with one molecule of acetonitrile (not shown) and a water molecule, which undergoes hydrogen bonding to both *N*-oxide groups. The two single crystal structures of *N,N'*-dioxide **33** demonstrate its ability to participate in hydrogen bonding and a considerable structural flexibility, which is expected to facilitate binding to molecules of varying geometry and size.

In sum, we have discovered and synthesized a class of axially chiral *N,N'*-dioxides exhibiting anti-parallel 3-substituted acridyl *N*-oxide moieties attached to the peri positions of naphthalene. The highly constrained C_2-symmetric framework was synthesized via CuO-mediated palladium-catalyzed Stille cross-coupling of dibromonaphthalene and 3-(3,5-dimethylphenyl)-9-trimethylstannylacridine. Oxidation gave fluorescent 1,8-bis(3,3'-(3,5-dimethylphenyl)-9,9'-diacridyl)naphthalene *N,N'*-dioxide, which was found to differentiate between the enantiomers of *N*-t-Boc-valine and *anti*-diaminocyclohexane. Single crystal structure analysis and fluorescence titration experiments showed that this new fluorosensor affords a flexible structure that is likely to facilitate stereoselective hydrogen bonding to a variety of chiral compounds.

Enantioselective Sensor Studies

Exhibiting two anti-parallel, selectively substituted acridyl moieties, *N,N'*-dioxide **33** is designed to undergo stereoselective recognition of chiral compounds measurable by fluorescence spectroscopy. Fluorescence studies of *N,N'*-dioxide **33** in acetonitrile revealed an emission maximum at 567 nm. Molecular modeling and X-ray analysis suggested that **33** would undergo strong interactions with hydrogen bond donors such as diamines or amino acids which would result in either a shift of the fluorescence emission maximum or a change in fluorescence intensity.

Based on the C_2-symmetry of **33**, we decided to employ chiral bidentate analytes **34** and **35** in fluorescence titration experiments. Titration studies using one isolated enantiomer of **33** at 3.5×10^{-5} M (excitation at 475 nm, emission maximum at 571 nm) and various amounts of (*R*)- and (*S*)-*N*-*t*-Boc-valine, **33**, in toluene showed enantioselective fluorescence quenching and a

remarkably high enantioselectivity factor (K^S_{sv}/K^R_{sv}) of 1.63, Figure 29. Moreover, the change of the fluorescence response of *N,N'*-dioxide **33** in the presence of 5.9×10^{-3} M *N-t*-Boc-valine was found to decrease linearly as the enantiopurity of (*S*)-**34** increases, Figure 30. By contrast, Stern-Völmer plots using *trans*-1,2-diaminocyclohexane, **35**, in acetonitrile (excitation at 475 nm, emission maximum at 571 nm) revealed enantioselective fluorescence enhancement and an enantioselectivity factor (K^{RR}_{sv}/K^{SS}_{sv}) of 1.50, Figure 31.

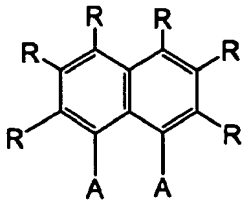
The data indicate the usefulness of sensors such as **33** for enantioselective sensing of hydrogen bond donors including alcohols, carboxylic acids, and amines. Based on our crystallographic data and PM3 calculations we postulate that the sensor's well-defined coordination geometry and C_2-symmetry allow rationalization and thus prediction of enantiodifferentiation. While the 3,5-dimethylphenyl groups occupy two quadrants of the coordination sphere of **33** and thus define its enantioselective cleft, the other two quadrants remain unoccupied (open). Coordination of a bidentate hydrogen bond donor such as **34** will be favored if the approaching enantiomer can place its *iso*propyl group into an open quadrant of the sensor while maintaining a preferentially populated low energy conformation, Figure 31. Thus, (*R,R*)-**33** is expected to form a more stable diastereomeric complex with (*R*)-**34**, whereas (*S*)-**34** experiences considerable steric repulsion because its *iso*propyl group is directed to an occupied quadrant of the selector, i.e. formation of an (*R,R*)-**33**-(*S*)-**34** adduct is energetically disfavored. While fluorescence enhancement is not well understood, enantioselective fluorescence quenching of excited *N,N'*-dioxide **33** in presence of amino acid **34** may be attributed to static quenching (i.e. constant fluorescence lifetimes) via non-radiative relaxation of diastereomeric hydrogen-bond adducts. We therefore assume that (*R*)-**34** is a more effective fluorescence quencher of (*R,R*)-**33** than (*S*)-**34**.

In sum, the linear fluorescence quenching effect in presence of *N*-t-Boc-valine was attributed to static quenching via non-radiative relaxation of diastereomeric hydrogen-bond complexes. The high sensitivity inherent to fluorescence spectroscopy combined with the considerable stereoselectivity of this new class of chemosensors affords a new tool for real-time analysis of the enantiomeric composition of chiral compounds. We assume that this new class of bidentate ligands provides a promising venue for developing new asymmetric Lewis acid and Lewis base catalysts. Axially chiral 1,8-diacridylnaphthalene *N,N'*-dioxides for enantioselective fluorosensing of mono- and bifunctional chiral compounds and applications in asymmetric

catalysis contemplated embodiments of the present invention.

Compounds of the Invention

One aspect of the present invention relates to a compound represented by formula **I**:



I

wherein

R represents independently for each occurrence H, alkyl, aryl, aralkyl, or alkenyl; and

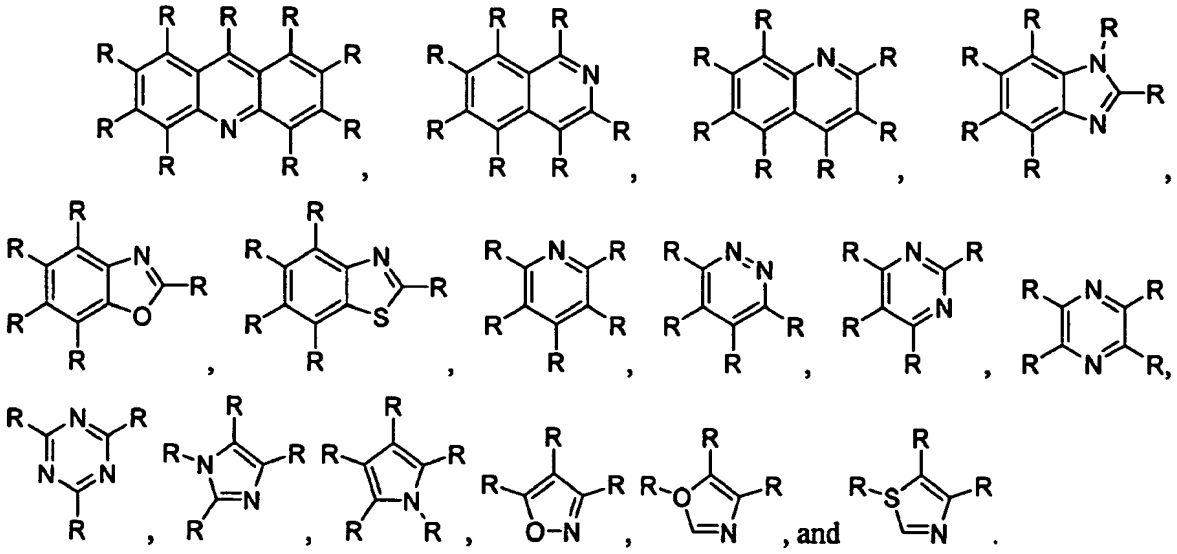
A represents independently for each occurrence aryl or heteroaryl.

In certain embodiments, the present invention relates to compound **I**, wherein R represents independently for each occurrence H or alkyl.

In certain embodiments, the present invention relates to compound **I**, wherein A is heteroaryl.

In certain embodiments, the present invention relates to compound **I**, wherein A is heteroaryl, and R represents independently for each occurrence H or alkyl.

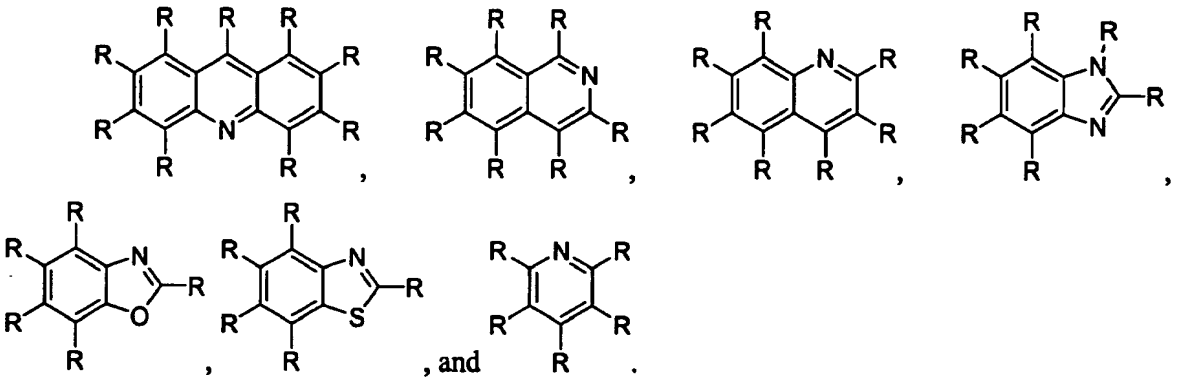
In certain embodiments, the present invention relates to compound **I**, wherein A is selected from the group consisting of:



wherein

R represents independently for each occurrence H, alkyl, aryl, or a bond to the nathphyl ring of the compound represented by formula I.

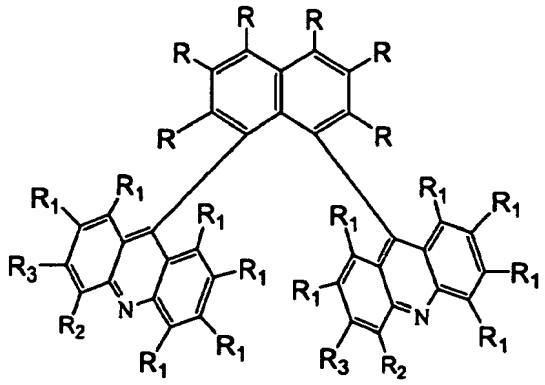
In certain embodiments, the present invention relates to compound I, wherein A is selected from the group consisting of:



wherein

R represents independently for each occurrence H, alkyl, aryl, or a bond to the nathphyl ring of the compound represented by formula I.

Another aspect of the present invention relates to a compound represented by formula II:



II

wherein

R, R_1, R_2, and R_3 represent independently for each occurrence H, alkyl, aryl, aralkyl, or alkenyl.

In certain embodiments, the present invention relates to compound **II**, wherein R represents independently for each occurrence H or alkyl.

In certain embodiments, the present invention relates to compound **II**, wherein R represents independently for each occurrence H.

In certain embodiments, the present invention relates to compound **II**, wherein R_1 represents independently for each occurrence H or alkyl.

In certain embodiments, the present invention relates to compound **II**, wherein R_1 represents independently for each occurrence H.

In certain embodiments, the present invention relates to compound **II**, wherein R_2 represents independently for each occurrence H, alkyl, or aryl.

In certain embodiments, the present invention relates to compound **II**, wherein R_2 represents independently for each occurrence alkyl.

In certain embodiments, the present invention relates to compound **II**, wherein R_2 represents independently for each occurrence methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, or pentyl.

In certain embodiments, the present invention relates to compound **II**, wherein R_2 represents independently for each occurrence methyl or isopropyl.

In certain embodiments, the present invention relates to compound **II**, wherein R_3 represents independently for each occurrence H, alkyl, or aryl.

In certain embodiments, the present invention relates to compound **II**, wherein R_3 represents independently for each occurrence aryl.

In certain embodiments, the present invention relates to compound **II**, wherein R_3 represents independently for each occurrence an optionally subsituted phenyl group.

In certain embodiments, the present invention relates to compound **II**, wherein R_3 represents independently for each occurrence 3,5-dimethylphenyl.

In certain embodiments, the present invention relates to compound **II**, wherein R is H, R_1 is H, R_3 is H, and R_2 is alkyl.

In certain embodiments, the present invention relates to compound **II**, wherein R is H, R_1 is H, R_3 is H, and R_2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, or pentyl.

In certain embodiments, the present invention relates to compound **II**, wherein R is H, R_1 is H, R_3 is H, and R_2 is methyl.

In certain embodiments, the present invention relates to compound **II**, wherein R is H, R_1 is H, R_3 is H, and R_2 is isopropyl.

In certain embodiments, the present invention relates to compound **II**, wherein R is H, R_1 is H, R_2 is H, and R_3 represents independently for each occurrence aryl.

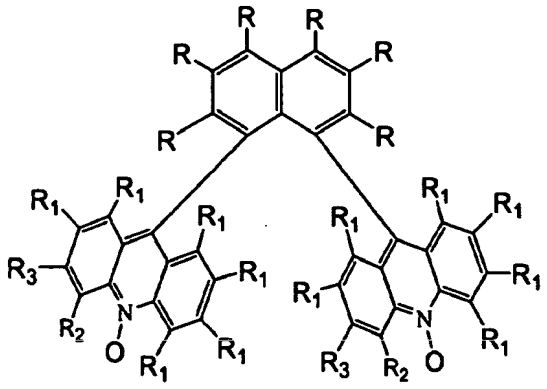
In certain embodiments, the present invention relates to compound **II**, wherein R is H, R_1 is H, R_2 is H, and R_3 represents independently for each occurrence an optionally substituted phenyl group.

In certain embodiments, the present invention relates to compound **II**, wherein R is H, R_1 is H, R_2 is H, and R_3 is 3,5-dimethylphenyl.

In certain embodiments, the present invention relates to compound **II**, wherein said compound is a chiral.

In certain embodiments, the present invention relates to compound **II**, wherein said compound is a single diastereomer.

Another aspect of the present invention relates to a compound represented by formula **III**:



III

wherein

R, R_1, R_2, and R_3 represent independently for each occurrence H, alkyl, aryl, aralkyl, or alkenyl.

In certain embodiments, the present invention relates to compound **III**, wherein R represents independently for each occurrence H or alkyl.

In certain embodiments, the present invention relates to compound **III**, wherein R represents independently for each occurrence H.

In certain embodiments, the present invention relates to compound **III**, wherein R_1 represents independently for each occurrence H or alkyl.

In certain embodiments, the present invention relates to compound **III**, wherein R_1 represents independently for each occurrence H.

In certain embodiments, the present invention relates to compound **III**, wherein R_2 represents independently for each occurrence H, alkyl, or aryl.

In certain embodiments, the present invention relates to compound **III**, wherein R_2 represents independently for each occurrence alkyl.

In certain embodiments, the present invention relates to compound **III**, wherein R_2 represents independently for each occurrence methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, or pentyl.

In certain embodiments, the present invention relates to compound **III**, wherein R_3 represents independently for each occurrence H, alkyl, or aryl.

In certain embodiments, the present invention relates to compound **III**, wherein R_3 represents independently for each occurrence aryl.

In certain embodiments, the present invention relates to compound **III**, wherein R_3 represents independently for each occurrence an optionally subsituted phenyl group.

In certain embodiments, the present invention relates to compound **III**, wherein R_3 represents independently for each occurrence 3,5-dimethylphenyl.

In certain embodiments, the present invention relates to compound **III**, wherein R is H, R_1 is H, R_3 is H, and R_2 is alkyl.

In certain embodiments, the present invention relates to compound **III**, wherein R is H, R_1 is H, R_3 is H, and R_2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, or pentyl.

In certain embodiments, the present invention relates to compound **III**, wherein R is H, R_1 is H, R_3 is H, and R_2 is methyl.

In certain embodiments, the present invention relates to compound **III**, wherein R is H, R_1 is H, R_3 is H, and R_2 is isopropyl.

In certain embodiments, the present invention relates to compound **III**, wherein R is H, R_1 is H, R_2 is H, and R_3 represents independently for each occurrence aryl.

In certain embodiments, the present invention relates to compound **III**, wherein R is H, R_1 is H, R_2 is H, and R_3 represents independently for each occurrence an optionally substituted phenyl group.

In certain embodiments, the present invention relates to compound **III**, wherein R is H, R_1 is H, R_2 is H, and R_3 is 3,5-dimethylphenyl.

In certain embodiments, the present invention relates to compound **III**, wherein said compound is a single enantiomer.

Methods of the Invention

One aspect of the present invention relates to a method of detecting an analyte, comprising the step of:

contacting an analyte with a compound of formula **II**, and comparing the fluorescence of said compound **II** in the presence of said analyte to the fluoresence of said compound **II** in the absence of said analyte.

In certain embodiments, the present invention relates to the aforementioned method, wherein the analyte is a cation.

In certain embodiments, the present invention relates to the aforementioned method, wherein the analyte is a alkali, alkaline earth, or transition metal ion.

In certain embodiments, the present invention relates to the aforementioned method, wherein the analyte is a alkali or alkaline earth metal ion.

In certain embodiments, the present invention relates to the aforementioned method, wherein the analyte is a lithium, sodium, potassium, magnesium, calcium, or strontium metal ion.

In certain embodiments, the present invention relates to the aforementioned method, wherein the analyte is a sodium, potassium, or calcium metal ion.

In certain embodiments, the present invention relates to the aforementioned method, wherein the analyte is a transition metal ion.

In certain embodiments, the present invention relates to the aforementioned method, wherein the analyte is a copper, iron, nickel, manganese, cobalt, chromium, vanadium, titanium, zirconium, rhodium, palladium, silver, cadmium, mercury, gold, platinum, or hafnium ion.

In certain embodiments, the present invention relates to the aforementioned method, wherein the analyte is a copper, iron, nickel, or manganese ion.

In certain embodiments, the present invention relates to the aforementioned method, wherein the analyte is a copper ion.

In certain embodiments, the present invention relates to the aforementioned method, wherein the analyte is a Cu^{2+}.

In certain embodiments, the present invention relates to the aforementioned method, wherein said compound of formula **II** is as defined in any one of the above embodiments.

Another aspect of the present invention relates to a method of detecting an analyte, comprising the step of:

contacting an analyte with a compound of formula **III**, and comparing the fluorescence of said compound **III** in the presence of said analyte to the fluoresence of said compound **III** in the absence of said analyte.

In certain embodiments, the present invention relates to the aforementioned method, wherein the analyte is a compound that comprises a hydrogen atom capable of participating in a hydrogen bond.

In certain embodiments, the present invention relates to the aforementioned method, wherein the analyte is a compound that comprises a hydroxyl, carboxylic acid, amine, amide, thiol, or percarboxylic acid functional group.

In certain embodiments, the present invention relates to the aforementioned method, wherein the analyte is a compound that comprises a hydroxyl, carboxylic acid, or amine functional group.

In certain embodiments, the present invention relates to the aforementioned method, wherein the analyte is a compound that comprises a hydroxyl functional group.

In certain embodiments, the present invention relates to the aforementioned method, wherein the analyte is a compound that comprises a carboxylic acid functional group.

In certain embodiments, the present invention relates to the aforementioned method, wherein the analyte is a chiral compound that comprises a hydrogen atom capable of participating in a hydrogen bond.

In certain embodiments, the present invention relates to the aforementioned method, wherein the analyte is a chiral compound that comprises a hydroxyl, carboxylic acid, amine, amide, thiol, or percarboxylic acid functional group.

In certain embodiments, the present invention relates to the aforementioned method, wherein the analyte is a chiral compound that comprises a hydroxyl, carboxylic acid, or amine functional group.

In certain embodiments, the present invention relates to the aforementioned method, wherein the analyte is a chiral compound that comprises a hydroxyl functional group.

In certain embodiments, the present invention relates to the aforementioned method, wherein the analyte is a chiral compound that comprises a carboxylic acid functional group.

In certain embodiments, the present invention relates to the aforementioned method, wherein said compound of formula **III** is as defined in any one of the above embodiments.

Definitions

For convenience, certain terms employed in the specification, examples, and appended claims are collected here.

The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are boron, nitrogen, oxygen, phosphorus, sulfur and selenium.

The term "alkyl" refers to the radical of saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In preferred embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C_1-C_{30} for straight chain, C_3-C_{30} for branched chain), and more preferably 20 or fewer. Likewise, preferred cycloalkyls have from 3-10 carbon atoms in their ring structure, and more preferably have 5, 6 or 7 carbons in the ring structure.

Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group, as defined above, but having from one to ten carbons, more preferably from one to six carbon atoms in its backbone structure. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths. Preferred alkyl groups are lower alkyls. In preferred embodiments, a substituent designated herein as alkyl is a lower alkyl.

The term "aralkyl", as used herein, refers to an alkyl group substituted with an aryl group (e.g., an aromatic or heteroaromatic group).

The terms "alkenyl" and "alkynyl" refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

The term "aryl" as used herein includes 5-, 6- and 7-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, anthracene, naphthalene, pyrene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles" or "heteroaromatics." The aromatic ring can be substituted at one or more ring positions with such substituents as described above, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, $-CF_3$, -CN, or the like. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls.

The terms *ortho*, *meta* and *para* apply to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and *ortho*-dimethylbenzene are synonymous.

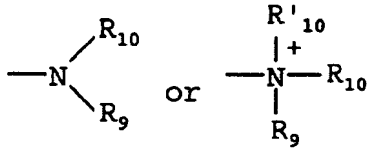
The terms "heterocyclyl" or "heterocyclic group" refer to 3- to 10-membered ring structures, more preferably 3- to 7-membered rings, whose ring structures include one to four heteroatoms. Heterocycles can also be polycycles. Heterocyclyl groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine,

furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic ring can be substituted at one or more positions with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, or the like.

The terms "polycyclyl" or "polycyclic group" refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, or the like.

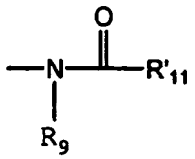
As used herein, the term "nitro" means $-NO_2$; the term "halogen" designates -F, -Cl, -Br or -I; the term "sulfhydryl" means -SH; the term "hydroxyl" means -OH; and the term "sulfonyl" means $-SO_2-$.

The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines, e.g., a moiety that can be represented by the general formula:



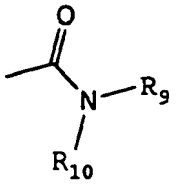
wherein R_9, R_{10} and R'_{10} each independently represent a group permitted by the rules of valence.

The term "acylamino" is art-recognized and refers to a moiety that can be represented by the general formula:



wherein R_9 is as defined above, and R'_{11} represents a hydrogen, an alkyl, an alkenyl or $-(CH_2)_m-R_8$, where m and R_8 are as defined above.

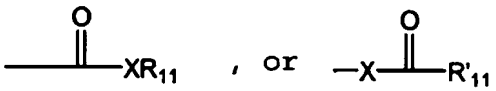
The term "amido" is art recognized as an amino-substituted carbonyl and includes a moiety that can be represented by the general formula:



wherein R_9, R_{10} are as defined above. Preferred embodiments of the amide will not include imides which may be unstable.

The term "alkylthio" refers to an alkyl group, as defined above, having a sulfur radical attached thereto. In preferred embodiments, the "alkylthio" moiety is represented by one of -S-alkyl, -S-alkenyl, -S-alkynyl, and $-S-(CH_2)_m-R_8$, wherein m and R_8 are defined above. Representative alkylthio groups include methylthio, ethyl thio, and the like.

The term "carbonyl" is art recognized and includes such moieties as can be represented by the general formula:

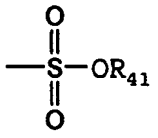


wherein X is a bond or represents an oxygen or a sulfur, and R_{11} represents a hydrogen, an alkyl, an alkenyl, $-(CH_2)_m-R_8$ or a pharmaceutically acceptable salt, R'_{11} represents a hydrogen, an alkyl, an alkenyl or $-(CH_2)_m-R_8$, where m and R_8 are as defined above. Where X is an oxygen and R_{11} or R'_{11} is not hydrogen, the formula represents an "ester". Where X is an oxygen, and R_{11} is as defined above, the moiety is referred to herein as a carboxyl group, and particularly when R_{11} is a hydrogen, the formula represents a "carboxylic acid". Where X is an oxygen, and R'_{11} is hydrogen, the formula represents a "formate". In general, where the oxygen atom of the above formula is replaced by sulfur, the formula represents a "thiolcarbonyl" group.

Where X is a sulfur and R_{11} or R'_{11} is not hydrogen, the formula represents a "thiolester." Where X is a sulfur and R_{11} is hydrogen, the formula represents a "thiolcarboxylic acid." Where X is a sulfur and R_{11}' is hydrogen, the formula represents a "thiolformate." On the other hand, where X is a bond, and R_{11} is not hydrogen, the above formula represents a "ketone" group. Where X is a bond, and R_{11} is hydrogen, the above formula represents an "aldehyde" group.

The terms "alkoxyl" or "alkoxy" as used herein refers to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. An "ether" is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxyl, such as can be represented by one of -O-alkyl, -O-alkenyl, -O-alkynyl, -O-$(CH_2)_m$-R_8, where m and R_8 are described above.

The term "sulfonate" is art recognized and includes a moiety that can be represented by the general formula:

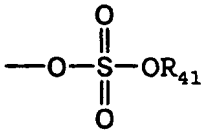


in which R_{41} is an electron pair, hydrogen, alkyl, cycloalkyl, or aryl.

The terms triflyl, tosyl, mesyl, and nonaflyl are art-recognized and refer to trifluoromethanesulfonyl, *p*-toluenesulfonyl, methanesulfonyl, and nonafluorobutanesulfonyl groups, respectively. The terms triflate, tosylate, mesylate, and nonaflate are art-recognized and refer to trifluoromethanesulfonate ester, *p*-toluenesulfonate ester, methanesulfonate ester, and nonafluorobutanesulfonate ester functional groups and molecules that contain said groups, respectively.

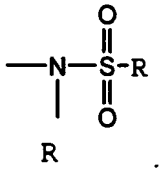
The abbreviations Me, Et, Ph, Tf, Nf, Ts, Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, nonafluorobutanesulfonyl, *p*-toluenesulfonyl and methanesulfonyl, respectively. A more comprehensive list of the abbreviations utilized by organic chemists of ordinary skill in the art appears in the first issue of each volume of the *Journal of Organic Chemistry*; this list is typically presented in a table entitled Standard List of Abbreviations. The abbreviations contained in said list, and all abbreviations utilized by organic chemists of ordinary skill in the art are hereby incorporated by reference.

The term "sulfate" is art recognized and includes a moiety that can be represented by the general formula:

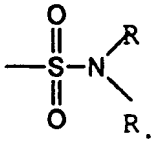


in which R_{41} is as defined above.

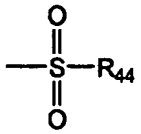
The term "sulfonylamino" is art recognized and includes a moiety that can be represented by the general formula:



The term "sulfamoyl" is art-recognized and includes a moiety that can be represented by the general formula:

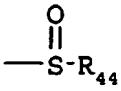


The term "sulfonyl", as used herein, refers to a moiety that can be represented by the general formula:



in which R_{44} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl.

The term "sulfoxido" as used herein, refers to a moiety that can be represented by the general formula:



in which R_{44} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aralkyl, or aryl.

A "selenoalkyl" refers to an alkyl group having a substituted seleno group attached thereto. Exemplary "selenoethers" which may be substituted on the alkyl are selected from one of -Se-alkyl, -Se-alkenyl, -Se-alkynyl, and -Se-$(CH_2)_m$-R_7, m and R_7 being defined above.

Analogous substitutions can be made to alkenyl and alkynyl groups to produce, for example, aminoalkenyls, aminoalkynyls, amidoalkenyls, amidoalkynyls, iminoalkenyls, iminoalkynyls, thioalkenyls, thioalkynyls, carbonyl-substituted alkenyls or alkynyls.

As used herein, the definition of each expression, e.g. alkyl, m, n, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein above. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds.

The phrase "protecting group" as used herein means temporary substituents which protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones, respectively. The field of protecting group chemistry has been reviewed (Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991).

Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

Contemplated equivalents of the compounds described above include compounds which otherwise correspond thereto, and which have the same general properties thereof (e.g., functioning as analgesics), wherein one or more simple variations of substituents are made which do not adversely affect the efficacy of the compound in binding to sigma receptors. In general, the compounds of the present invention may be prepared by the methods illustrated in the general reaction schemes as, for example, described below, or by modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are in themselves known, but are not mentioned here.

For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover.

Combinatorial Libraries

The subject compounds may be synthesized using the methods of combinatorial synthesis described in this section. Combinatorial libraries of the compounds may be used for the screening of pharmaceutical, agrochemical or other biological or medically-related activity or material-related qualities. A combinatorial library for the purposes of the present invention is a mixture of chemically related compounds which may be screened together for a desired property; said libraries may be in solution or covalently linked to a solid support. The preparation of many related compounds in a single reaction greatly reduces and simplifies the number of screening processes which need to be carried out. Screening for the appropriate biological, pharmaceutical, agrochemical or physical property may be done by conventional methods.

Diversity in a library can be created at a variety of different levels. For instance, the substrate aryl groups used in a combinatorial approach can be diverse in terms of the core aryl moiety, e.g., a variegation in terms of the ring structure, and/or can be varied with respect to the other substituents.

A variety of techniques are available in the art for generating combinatorial libraries of small organic molecules. See, for example, Blondelle et al. (1995) Trends Anal. Chem. 14:83; the Affymax U.S. Patents 5,359,115 and 5,362,899: the Ellman U.S. Patent 5,288,514: the Still et al. PCT publication WO 94/08051; Chen et al. (1994) JACS 116:2661: Kerr et al. (1993) JACS 115:252; PCT publications WO92/10092, WO93/09668 and WO91/07087; and the Lerner et al. PCT publication WO93/20242). Accordingly, a variety of libraries on the order of about 16 to 1,000,000 or more diversomers can be synthesized and screened for a particular activity or property.

In an exemplary embodiment, a library of substituted diversomers can be synthesized using the subject reactions adapted to the techniques described in the Still et al. PCT publication WO 94/08051, e.g., being linked to a polymer bead by a hydrolyzable or photolyzable group, e.g., located at one of the positions of substrate. According to the Still et al. technique, the library is synthesized on a set of beads, each bead including a set of tags identifying the particular diversomer on that bead. In one embodiment, which is particularly suitable for discovering enzyme inhibitors, the beads can be dispersed on the surface of a permeable membrane, and the diversomers released from the beads by lysis of the bead linker. The diversomer from each bead will diffuse across the membrane to an assay zone, where it will

interact with an enzyme assay. Detailed descriptions of a number of combinatorial methodologies are provided below.

A. Direct Characterization

A growing trend in the field of combinatorial chemistry is to exploit the sensitivity of techniques such as mass spectrometry (MS), e.g., which can be used to characterize sub-femtomolar amounts of a compound, and to directly determine the chemical constitution of a compound selected from a combinatorial library. For instance, where the library is provided on an insoluble support matrix, discrete populations of compounds can be first released from the support and characterized by MS. In other embodiments, as part of the MS sample preparation technique, such MS techniques as MALDI can be used to release a compound from the matrix, particularly where a labile bond is used originally to tether the compound to the matrix. For instance, a bead selected from a library can be irradiated in a MALDI step in order to release the diversomer from the matrix, and ionize the diversomer for MS analysis.

B) Multipin Synthesis

The libraries of the subject method can take the multipin library format. Briefly, Geysen and co-workers (Geysen et al. (1984) PNAS 81:3998-4002) introduced a method for generating compound libraries by a parallel synthesis on polyacrylic acid-grated polyethylene pins arrayed in the microtitre plate format. The Geysen technique can be used to synthesize and screen thousands of compounds per week using the multipin method, and the tethered compounds may be reused in many assays. Appropriate linker moieties can also been appended to the pins so that the compounds may be cleaved from the supports after synthesis for assessment of purity and further evaluation (c.f., Bray et al. (1990) Tetrahedron Lett 31:5811-5814; Valerio et al. (1991) Anal Biochem 197:168-177; Bray et al. (1991) Tetrahedron Lett 32:6163-6166).

C) Divide-Couple-Recombine

In yet another embodiment, a variegated library of compounds can be provided on a set of beads utilizing the strategy of divide-couple-recombine (see, e.g., Houghten (1985) PNAS 82:5131-5135; and U.S. Patents 4,631,211; 5,440,016; 5,480,971). Briefly, as the name implies, at each synthesis step where degeneracy is introduced into the library, the beads are divided into separate groups equal to the number of different substituents to be added at a particular position

in the library, the different substituents coupled in separate reactions, and the beads recombined into one pool for the next iteration.

In one embodiment, the divide-couple-recombine strategy can be carried out using an analogous approach to the so-called "tea bag" method first developed by Houghten, where compound synthesis occurs on resin sealed inside porous polypropylene bags (Houghten et al. (1986) PNAS 82:5131-5135). Substituents are coupled to the compound-bearing resins by placing the bags in appropriate reaction solutions, while all common steps such as resin washing and deprotection are performed simultaneously in one reaction vessel. At the end of the synthesis, each bag contains a single compound.

D) Combinatorial Libraries by Light-Directed, Spatially Addressable Parallel Chemical Synthesis

A scheme of combinatorial synthesis in which the identity of a compound is given by its locations on a synthesis substrate is termed a spatially-addressable synthesis. In one embodiment, the combinatorial process is carried out by controlling the addition of a chemical reagent to specific locations on a solid support (Dower et al. (1991) Annu Rep Med Chem 26:271-280; Fodor, S.P.A. (1991) Science 251:767; Pirrung et al. (1992) U.S. Patent No. 5,143,854; Jacobs et al. (1994) Trends Biotechnol 12:19-26). The spatial resolution of photolithography affords miniaturization. This technique can be carried out through the use protection/deprotection reactions with photolabile protecting groups.

The key points of this technology are illustrated in Gallop et al. (1994) J Med Chem 37:1233-1251. A synthesis substrate is prepared for coupling through the covalent attachment of photolabile nitroveratryloxycarbonyl (NVOC) protected amino linkers or other photolabile linkers. Light is used to selectively activate a specified region of the synthesis support for coupling. Removal of the photolabile protecting groups by light (deprotection) results in activation of selected areas. After activation, the first of a set of amino acid analogs, each bearing a photolabile protecting group on the amino terminus, is exposed to the entire surface. Coupling only occurs in regions that were addressed by light in the preceding step. The reaction is stopped, the plates washed, and the substrate is again illuminated through a second mask, activating a different region for reaction with a second protected building block. The pattern of masks and the sequence of reactants define the products and their locations. Since this process

utilizes photolithography techniques, the number of compounds that can be synthesized is limited only by the number of synthesis sites that can be addressed with appropriate resolution. The position of each compound is precisely known; hence, its interactions with other molecules can be directly assessed.

In a light-directed chemical synthesis, the products depend on the pattern of illumination and on the order of addition of reactants. By varying the lithographic patterns, many different sets of test compounds can be synthesized simultaneously; this characteristic leads to the generation of many different masking strategies.

E) Encoded Combinatorial Libraries

In yet another embodiment, the subject method utilizes a compound library provided with an encoded tagging system. A recent improvement in the identification of active compounds from combinatorial libraries employs chemical indexing systems using tags that uniquely encode the reaction steps a given bead has undergone and, by inference, the structure it carries. Conceptually, this approach mimics phage display libraries, where activity derives from expressed peptides, but the structures of the active peptides are deduced from the corresponding genomic DNA sequence. The first encoding of synthetic combinatorial libraries employed DNA as the code. A variety of other forms of encoding have been reported, including encoding with sequenceable bio-oligomers (e.g., oligonucleotides and peptides), and binary encoding with additional non-sequenceable tags.

1) Tagging with sequenceable bio-oligomers

The principle of using oligonucleotides to encode combinatorial synthetic libraries was described in 1992 (Brenner et al. (1992) PNAS 89:5381-5383), and an example of such a library appeared the following year (Needles et al. (1993) PNAS 90:10700-10704). A combinatorial library of nominally 7^7 (= 823,543) peptides composed of all combinations of Arg, Gln, Phe, Lys, Val, D-Val and Thr (three-letter amino acid code), each of which was encoded by a specific dinucleotide (TA, TC, CT, AT, TT, CA and AC, respectively), was prepared by a series of alternating rounds of peptide and oligonucleotide synthesis on solid support. In this work, the amine linking functionality on the bead was specifically differentiated toward peptide or oligonucleotide synthesis by simultaneously preincubating the beads with

reagents that generate protected OH groups for oligonucleotide synthesis and protected NH_2 groups for peptide synthesis (here, in a ratio of 1:20). When complete, the tags each consisted of 69-mers, 14 units of which carried the code. The bead-bound library was incubated with a fluorescently labeled antibody, and beads containing bound antibody that fluoresced strongly were harvested by fluorescence-activated cell sorting (FACS). The DNA tags were amplified by PCR and sequenced, and the predicted peptides were synthesized. Following such techniques, compound libraries can be derived for use in the subject method, where the oligonucleotide sequence of the tag identifies the sequential combinatorial reactions that a particular bead underwent, and therefore provides the identity of the compound on the bead.

The use of oligonucleotide tags permits exquisitely sensitive tag analysis. Even so, the method requires careful choice of orthogonal sets of protecting groups required for alternating co-synthesis of the tag and the library member. Furthermore, the chemical lability of the tag, particularly the phosphate and sugar anomeric linkages, may limit the choice of reagents and conditions that can be employed for the synthesis of non-oligomeric libraries. In preferred embodiments, the libraries employ linkers permitting selective detachment of the test compound library member for assay.

Peptides have also been employed as tagging molecules for combinatorial libraries. Two exemplary approaches are described in the art, both of which employ branched linkers to solid phase upon which coding and ligand strands are alternately elaborated. In the first approach (Kerr JM et al. (1993) J Am Chem Soc 115:2529-2531), orthogonality in synthesis is achieved by employing acid-labile protection for the coding strand and base-labile protection for the compound strand.

In an alternative approach (Nikolaiev et al. (1993) Pept Res 6:161-170), branched linkers are employed so that the coding unit and the test compound can both be attached to the same functional group on the resin. In one embodiment, a cleavable linker can be placed between the branch point and the bead so that cleavage releases a molecule containing both code and the compound (Ptek et al. (1991) Tetrahedron Lett 32:3891-3894). In another embodiment, the cleavable linker can be placed so that the test compound can be selectively separated from the bead, leaving the code behind. This last construct is particularly valuable because it permits screening of the test compound without potential interference of the coding groups. Examples in

the art of independent cleavage and sequencing of peptide library members and their corresponding tags has confirmed that the tags can accurately predict the peptide structure.

2) Non-sequenceable Tagging: Binary Encoding

An alternative form of encoding the test compound library employs a set of non-sequencable electrophoric tagging molecules that are used as a binary code (Ohlmeyer et al. (1993) PNAS 90:10922-10926). Exemplary tags are haloaromatic alkyl ethers that are detectable as their trimethylsilyl ethers at less than femtomolar levels by electron capture gas chromatography (ECGC). Variations in the length of the alkyl chain, as well as the nature and position of the aromatic halide substituents, permit the synthesis of at least 40 such tags, which in principle can encode 2^{40} (e.g., upwards of 10^{12}) different molecules. In the original report (Ohlmeyer et al., supra) the tags were bound to about 1% of the available amine groups of a peptide library via a photocleavable o-nitrobenzyl linker. This approach is convenient when preparing combinatorial libraries of peptide-like or other amine-containing molecules. A more versatile system has, however, been developed that permits encoding of essentially any combinatorial library. Here, the compound would be attached to the solid support via the photocleavable linker and the tag is attached through a catechol ether linker via carbene insertion into the bead matrix (Nestler et al. (1994) J Org Chem 59:4723-4724). This orthogonal attachment strategy permits the selective detachment of library members for assay in solution and subsequent decoding by ECGC after oxidative detachment of the tag sets.

Although several amide-linked libraries in the art employ binary encoding with the electrophoric tags attached to amine groups, attaching these tags directly to the bead matrix provides far greater versatility in the structures that can be prepared in encoded combinatorial libraries. Attached in this way, the tags and their linker are nearly as unreactive as the bead matrix itself. Two binary-encoded combinatorial libraries have been reported where the electrophoric tags are attached directly to the solid phase (Ohlmeyer et al. (1995) PNAS 92:6027-6031) and provide guidance for generating the subject compound library. Both libraries were constructed using an orthogonal attachment strategy in which the library member was linked to the solid support by a photolabile linker and the tags were attached through a linker cleavable only by vigorous oxidation. Because the library members can be repetitively partially photoeluted from the solid support, library members can be utilized in multiple assays.

Successive photoelution also permits a very high throughput iterative screening strategy: first, multiple beads are placed in 96-well microtiter plates; second, compounds are partially detached and transferred to assay plates; third, a metal binding assay identifies the active wells; fourth, the corresponding beads are rearrayed singly into new microtiter plates; fifth, single active compounds are identified; and sixth, the structures are decoded.

Exemplification

The invention now being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

Example 1

General Procedures

All reaction were carried out under nitrogen. Commercially available reagents and solvents were used without further purification. Flash chromatography was carried out on silica gel (particle size 0.032-0.063mm). NMR spectra were obtained at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR) using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm relative to TMS. Elemental analysis data were collected using a Perkin Elmer 2400 CHN. UV measurements were performed on an Agilent 8453 UV-Visible spectrometer. Extinction coefficients were determined from 5 different measurements in CH_2Cl_2. Absorption and emission spectra were collected under nitrogen. Fluorescence experiments were conducted using a Fluoromax-2 from Instruments S.A. Inc. Quantum yields of **2** and **3** were determined in benzene following literature procedures. See Jones II, G.; Jackson, W. R.; Choi, C.-Y. *J. Phys. Chem.* **1985**, *89*, 294-300. 1,8-Bis(4,4'-dialkyl-9,9'-diacridyl)naphthalenes were excited at 381nm and relative integrated intensities of the emission spectra were compared to anthracene. The quantum efficiency of anthracene in benzene (25.6%) was taken from the literature.

Synthetic Procedures

1,8-Bis(4,4'-dimethyl-9,9'-diacridyl)naphthalene, 2

A mixture 1,8-dibromonaphthanene **1** (92 mg, 0.32 mmol), tetrakis(triphenylphosphine)palladium(0) (0.11 g, 0.10 mmol, 30mol%), and CuO (51 mg, 0.64 mmol) in 10 mL DMF was stirred at 140°C. After 5 min, a solution of 4-methyl-9-trimethylstannanyl acridine **12** (0.46 g, 1.29 mmol) dissolved in 2 mL of DMF was added in one portion. After 16 hours, the reaction mixture was quenched with 10% aqueous ammonium hydroxide, extracted with diethyl ether, dried over $MgSO_4$ and concentrated in vacuo. Purification of the orange residue by flash chromatography (100:5:1 hexanes:ethyl acetate:triethylamine) afforded **2** (41 mg, 25 %) as a yellow solid. The diastereoisomers were separated on a Phenylglycine column (250 mm x 4.6 mm) using hexanes/EtOH (98:2) as the mobile phase. The *anti-* and *syn*-conformation of the two isomer of **2** was determined by ^{1}H-NMR spectroscopy using 1.2 mol equivalents of (+)-Eu(tfc)$_3$ as a chiral shift reagent. *anti-*Isomer: ^{1}H-NMR δ = 2.72 (s, 6H), 6.50 (d, J = 8.8 Hz, 1H), 6.52 (d, J = 8.8 Hz, 1H), 6.58-6.78 (m, 6H), 7.18 (d, J = 6.6 Hz, 2H), 7.22-7.27 (m, 2H), 7.35 (ddd, J = 1.7 Hz, J = 7.8 Hz, J = 8.8 Hz, 2H), 7.68-7.73 (m, 4H), 8.25 (dd, J = 1.3 Hz, J = 8.8 Hz, 2H). ^{13}C-NMR δ = 18.87, 123.75, 124.67, 125.00, 125.70, 125.74, 128.18, 128.37, 129.72, 129.87, 130.58, 130.73, 134.37, 135.10, 135.90, 146.73, 146.81, 146.04, 146.32. LC/APCI/MS: m/z = 511(M + H). *syn*-Isomer: ^{1}H-NMR δ = 2.67 (s, 6H), 6.45-6.52 (m, 2H), 6.58-6.70 (m, 4H), 6.80 (d, J = 8.8 Hz 2H), 7.20-7.40 (m, 6H), 7.65-7.78 (m, 4H), 8.25 (dd, J = 1.3 Hz, J = 8.8 Hz, 2H). ^{13}C-NMR δ = 18.94, 123.42, 124.67, 125.00, 125.73, 125.76, 128.21, 128.41, 129.73, 129.85, 130.58, 130.73, 134.37, 135.10, 135.90, 146.72, 146.81, 146.04, 146.32. LC/APCI/MS: m/z = 511(M + H). Anal. calcd. for *syn* and *anti*-$C_{38}H_{26}N_2$: C, 89.38; H, 5.13; N, 5.49. Found: C, 89.80; H, 5.57; N, 4.99.

1,8-Bis(4,4'-diisopropyl-9,9'-diacridyl)naphthalene, 3

A mixture 1,8-dibromonaphthanene **1** (0.25 g, 0.89 mmol), tetrakis(triphenylphosphine)palladium(0) (0.31 g, 0.27 mmol, 30mol %), and CuO (0.14 g, 1.78 mmol) in 18 mL DMF was stirred at 140°C. After 5 min, a solution of 4-isopropyl-9-trimethylstannanyl acridine **12** (1.45 g, 3.8 mmol) dissolved in 2 mL DMF was added in one portion. After 16 hours, the reaction mixture was quenched with 10% aqueous ammonium hydroxide, extracted with diethyl ether, dried over $MgSO_4$ and concentrated in vacuum. Purification of the orange residue by flash chromatography (100:5:1 hexanes:ethyl acetate:trimethylamine) afforded **3** (126 mg, 25 %) as a yellow solid. The diastereoisomers were

separated on a Phenylglycine column (250 mm x 4.6 mm) using hexanes/EtOH (98.4:1.6) as the mobile phase. Isomer 1: ^{1}H-NMR δ = 1.22 (d, *J* = 6.9 Hz, 6H), 1.52 (d, *J* = 6.9 Hz, 6H), 4.23 (sept, *J* = 6.9 Hz, 2H), 6.60-6.70 (m, 6H), 6.85 (d, *J* = 8.4 Hz, 2H), 7.18-7.30 (m, 6H), 7.60-7.78 (m, 4H), 8.26 (dd, *J* = 1.6 Hz, *J* = 8.4 Hz, 2H). ^{13}C-NMR δ = 24.38, 27.25, 27.33, 123.58, 123.96, 124.68, 124.74, 124.74, 125.54, 125.58, 125.87, 128.21, 129.72, 129.90, 130.92, 134.93, 135.10, 144.95, 145.01, 145.61, 145.97, 146.79. LC/APCI/MS: m/z = 567 (M + H). Isomer 2: ^{1}H-NMR δ = 1.22 (d, *J* = 6.9 Hz, 6H), 1.52 (d, *J* = 6.9 Hz, 6H), 4.23 (sept, *J* = 6.9 Hz, 2H), 6.59-6.78 (m, 6H), 7.20-7.37 (m, 8H), 7.64-7.72 (m, 4H), 8.26 (dd, *J* = 1.6 Hz, *J* = 8.4 Hz, 2H). ^{13}C-NMR δ = 24.62, 26.98, 27.08, 123.54, 123.95, 124.60, 124.71, 125.16, 125.52, 125.74, 128.09, 129.69, 129.93, 130.79, 134.59, 134.70, 144.95,145.01, 145.57, 145.77, 146.79. LC/APCI/MS: m/z = 567 (M + H). Anal. calcd. for *syn* and *anti*-$C_{42}H_{34}N_2$: C, 89.01; H, 6.05; N, 4.94. Found: C, 89.38; H, 6.25; N, 4.67.

2-(2'-Methylphenylamino)benzoic acid, 7

A mixture of 2-methylaniline (2.68 g, 25 mmol), 2-chlorobenzoic acid (3.8 g, 24 mmol), K_2CO_3 (4.1 g, 30 mmol), Cu powder (0.05 g), Cu_2O (0.05 g), and 5 mL 2-methoxyethanol was refluxed for 2 hours. The cooled reaction mixture was poured into 30 mL water. Charcoal was then added and the solution was filtrated through Celite. The crude product was obtained by acidification of the filtrate with diluted HCl at ambient temperature, and subsequent recrystallization from acetone/water (1/8). The crystals were dissolved in 100 mL 5 % aqueous Na_2CO_3. The solution was filtered through Celite and the product was precipitated by acidification to afford acid **7** (3.0 g, 55 %) as a white powder. ^{1}H-NMR δ = 2.29 (s, 3H), 6.72 (bs, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 7.12 (dd, *J* = 7.2Hz, *J* = 7.4Hz, 1H), 7.20-7.34 (m, 5H), 8.05 (d, *J* = 7.2 Hz, 1H), 9.18 (bs, 1H). ^{13}C-NMR δ = 18.96, 114.4, 117.3, 125.67, 125.98, 127.22, 127.49, 131.61, 131.85, 134.10, 135.79, 135.97, 139.16, 150.35.

2-(2'-Isopropylphenylamino)benzoic acid, 8

A mixture of 2-isopropylaniline (3.4 g, 25 mmol), 2-chlorobenzoic acid (3.8 g, 24 mmol), K_2CO_3 (4.1 g, 30 mmol), Cu powder (0.05 g), Cu_2O (0.05 g), in 5 mL 2-methoxyethanol was refluxed for 2 hours. The cooled reaction mixture was poured into 30 mL water. Charcoal was then added and the solution was filtrated through Celite. The crude product was obtained by acidification of the filtrate with diluted HCl at ambient temperature, and subsequent

recrystallization from acetone/water (1/8). The crystals were dissolved in 100 mL 5 % aqueous Na_2CO_3, filtered through Celite and the crystals were recrystallized by acidification to yield acid **8** (4.4 g, 73 %) as a white powder. ^{1}H-NMR δ = 1.22 (d, *J* = 6.9 Hz, 6H), 3.21 (sept, *J* = 6.9 Hz, 1H), 4.68 (bs, 1H), 6.68 (dd, *J* = 7.2 Hz, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 7.22-7.40 (m, 4H), 8.1 (dd, *J* = 1.7 Hz, *J* = 8.2 Hz, 1H), 9.18 (s, 1H). ^{13}C-NMR δ = 23.97, 28.83, 114.38, 117.09, 126.72, 126.90, 127.13, 127.31, 133.08, 135.68, 136.04, 137.84, 145.09, 151.20, 174.73.

9-Bromo-4-methylacridine, 9

2-(2'-Methylphenylamino)benzoic acid **7** (1.0 g, 4.4 mmol) was suspended in 11.0 g (38 mmol) of phosphorus oxybromide, and the mixture was heated to 120 °C for 2 hours. Excess phosphorus oxybromide was removed by distillation and the residual solution was poured into a 1:1 mixture of aqueous ammonium hydroxide:CH_2Cl_2. The CH_2Cl_2 solution was separated, dried, filtered, and the combined organic layers were dried in vacuo to give **9** (1.0 g, 85 %) as a yellow powder. ^{1}H-NMR δ = 2.94 (s, 3H), 7.53 (dd, *J* = 8.5 Hz, *J* = 8.8 Hz, 1H), 7.59-7.69 (m, 2H), 7.78 (ddd, *J* = 1.4 Hz, *J* = 8.5 Hz, *J* = 8.5 Hz, 1H), 8.28 (dd, *J* = 8.5 Hz, *J* = 8.5 Hz, 2H), 8.43 (dd, *J* = 1.4 Hz, *J* = 8.8 Hz, 1H). ^{13}C-NMR δ = 19.48, 126.37, 128.49, 128.76, 129.07, 129.28, 129.72, 130.95, 131.15, 131.88, 135.87, 138.12, 148.43, 148.71. Anal. calcd. for $C_{14}H_{10}NBr$: C, 61.79; H, 3.70; N, 5.15. Found: C, 61.40; H, 3.72; N, 5.05.

9-Bromo-4-isopropyl-acridine, 10

2-(2'-Isopropylphenylamino)benzoic acid **8** (1.0 g, 3.9 mmol) was suspended in 11.0 g (38 mmol) of phosphorus oxybromide, and the mixture was heated to 120 °C for 2 hours. Excess phosphorus oxybromide was removed by distillation and the residual solution was poured into a 1:1 mixture of aqueous ammonium hydroxide:CH_2Cl_2. The CH_2Cl_2 solution was separated, dried, filtered, and the combined organic layers was dried in vacuum to give **10** (1.2 g, 79 %) as yellow powder. ^{1}H-NMR δ = 1.45 (d, *J* = 6.9 Hz, 6H), 4.56 (sept, *J* = 6.9 Hz, 1H), 7.56-7.70 (m, 3H), 7.78 (ddd, *J* = 1.5 Hz, *J* = 6.6 Hz, *J* = 6.6 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 8.29 (dd, *J* = 1.5 Hz, *J* = 8.5 Hz, 1H), 8.41 (d, *J* = 8.8 Hz, 1H). ^{13}C-NMR δ = 24.00, 28.21, 125.20, 125.62, 125.86, 126.49, 127.38, 127.64, 129.90, 130.58, 130.83, 135.69, 147.44, 148.01, 148.14. Anal. calcd. for $C_{16}H_{14}NBr$: C, 64.02; H, 4.70; N, 4.67. Found: C, 64.23; H, 4.78; N, 4.59.

4-Methyl-9-trimethylstannanylacridine, 11

A solution of 9-bromo-4-methylacridine **9** (1 g, 3.7 mmol) in 50 ml anhydrous diethyl ether was cooled to -78°C under nitrogen. To the solution was added 1.6 M *n*-BuLi in hexanes (0.74 mmol, 0.46 mL) dropwise over a period of 15 min and a 1.0 M solution of Me_3SnCl in hexanes (0.81 mL, 0.81 mmol). The reaction solution mixture was allowed to warm to room temperature, stirred for 18 hours and concentrated in vacuo. Purification of the orange residue by flash chromatography (100:10:1 hexanes:ethyl acetate :triethyl amine) afforded **11** (1.1 g, 84 %) as a yellow solid. GC-MS revealed contamination of the product with 5-10% 4-methylacridine that could not be separated by chromatography. The stannane was therefore employed in the Stille coupling with 1,8-dibromonaphthalene without further purification. ^{1}H-NMR δ = 0.67 (s, 9H), 2.95 (s, 3H), 7.41 (dd, J = 6.9 Hz, J = 8.8 Hz, 1H), 7.52 (ddd, J = 1.4 Hz, J = 6.5 Hz, J = 6.5 Hz, 1H), 7.61 (d, J = 6.9 Hz, 1H), 7.74 (ddd, J = 1.4 Hz, J = 7.4 Hz, J = 7.4 Hz, 1H), 7.97 (d, J = 7.9 Hz, 1H), 8.12 (d, J = 9.3 Hz, 1H), 8.28 (d, J = 7.9 Hz, 1H). ^{13}C-NMR δ = -4.63, 19.51, 125.33, 125.56, 128.42, 128.94, 129.30, 129.93, 131.38, 133.49, 133.62, 138.58, 147.36, 147.53, 156.78.

4-Isopropyl-9-trimethylstannylacridine, 12

Stannane **12** (1.4 g, 3.5mmol) was obtained in 90 % yield using 9-bromo-4-isopropyl-acridine **10** (1.2 g, 3.9 mmol), 1.6 M *n*-BuLi in hexanes (2.6 mL, 4.2 mmol) and a 1.0 M solution of Me_3SnCl in hexanes (4.5 mL, 4.5 mmol) following the procedure described for the preparation of **11**. GC-MS revealed contamination of the product with 5-10% 4-isopropylacridine that could not be separated by chromatography. The stannane was therefore employed in the Stille coupling with 1,8-dibromonaphthalene without further purification. ^{1}H-NMR δ = 0.71 (s, 9H), 1.51 (d, J = 6.9 Hz, 6H), 4.69 (sept, J = 6.9 Hz, 1H), 7.48-7.60 (m, 2H), 7.67 (d, J = 6.4 Hz, 1H), 7.76 (ddd, J = 1.4 Hz, J = 6.0 Hz, J = 6.0 Hz, 1H), 8.02 (dd, J = 1.1 Hz, J = 8.6 Hz, 1H), 8.16 (d, J = 8.5 Hz, 1H), 8.33 (d, J = 8.8 Hz, 1H). ^{13}C-NMR δ = -4.05, 24.05, 28.02, 124.77, 125.37, 125.50, 128.05, 129.05, 129.95, 131.71,1 33.33, 133.72, 146.16, 147.18, 148.72, 156.59.

Example 2

General Procedures

All reactions were carried out under nitrogen. Commercially available reagents and solvents were used without further purification. 1,8-Dibromonaphthalene was prepared from 1,8-diaminonaphthalene as described in the literature. Seyferth, D.; Vick, S. C. *J. Organomet. Chem.* **1977**, *141*, 178-187. Flash chromatography was performed on silica gel (particle size 0.032-0.063mm). NMR spectra were obtained at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR) using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm relative to TMS. Elemental analysis data were collected using a Perkin Elmer 2400 CHN. Fluorescence experiments were conducted using a Fluoromax-2 from Instruments S.A. Inc. Absorption and emission spectra were collected under nitrogen. Circular dichroism spectra were obtained in hexane/ethyl alcohol 4:1 using a JASCO J-710 circular dichroism chiroptical spectrometer. Atmospheric pressure chemical ionization (APCI) mass spectra were collected on a YMC-Pack CN column (4.6 x 250 mm) using an HP 1100 HPLC/MSD equipped with electrospray and atmospheric pressure chemical ionization MS detection and hexanes/EtOH = 9:1 as the mobile phase. Chiral HPLC was carried out on an HP 1050 equipped with an autosampler and DAD detector using a Chiralpak AD column (250 mm x 4.6 mm, 5 μm) and hexanes/ethyl alcohol (4:1) as the mobile phase. Preparative separations were performed by repetitive injections of 50 μL of **16** dissolved in hexanes/EtOH (1:1) at a concentration of approximately 20 mg/mL. For analytical separations, **2** was dissolved in the same diluent at a concentration of 1 mg/mL and 10 μL were injected. Single crystal X-ray diffractions of *N,N'*-dioxide **16** were performed at -90 °C (**16**-CH_2Cl_2) and -87 °C (**16**-H_2O-CH_3CN) using a Siemens platform diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). The structures were solved by direct methods and refined with full-matrix least-squares/difference Fourier analysis using SHELX-97-2 software. Non-hydrogen atoms were refined with anisotropic displacement parameters and all hydrogen atoms were placed in calculated positions and refined with a riding model. Data were corrected for the affects of absorption using SADABS. Crystal data, collection parameters, refinement details, and key molecular parameters are shown in Table 1.

Synthetic Procedures

3-(3,5-dimethylphenyl)aniline, 9

To a solution of 3-bromoaniline, **8**, (17.2 g, 0.10 mol), 3,5-dimethylphenylboronic acid (16.5 g, 0.11 mol), CsF (50 g, 0.33 mol), $Pd_2(dba)_3$ (0.92 g, 5 mmol) in 50 mL anhydrous THF was added a solution of P(*t*-Bu)$_3$ (0.49 g, 2.4 mmol) in 3 mL of THF. The exothermal reaction was cooled using a water bath. The solution mixture was stirred at room temperature for 2 hours and concentrated in vacuo. The residue was dissolved in methylene chloride and washed with water. The combined organic layers were dried over $MgSO_4$ and solvents were evaporated. Purification of the orange residue by flash chromatography (100:10:1 hexanes:ethyl acetate:triethylamine) afforded **9** (20.0 g, 99 %) as a brown oil. ^{1}H-NMR δ = 2.30 (s, 6H), 3.53 (bs, 2H), 6.50 (dd, J = 2.5 Hz, 7.1 Hz, 1H), 6.77 (d, J = 1.6 Hz, 2.2 Hz, 1H), 6.91 (s, 1H), 6.94 (dd, J = 1.2 Hz, 2.5 Hz, 1H), 7.10-7.15 (m, 3H). ^{13}C-NMR δ = 22.2, 115.4, 119.3, 125.7, 129.5, 130.2, 138.7, 141.8, 143.3, 145.7. Anal. calcd. for $C_{14}H_{15}N$: C, 85.28; H, 7.61; N, 7.11. Found: C, 85.61; H, 8.01; N, 7.00.

N-3-(3,5-dimethylphenyl)anthranilic acid, 11

A mixture of 3-(3,5-dimethylphenyl)aniline **9** (5.3 g, 27 mmol), 2-chlorobenzoic acid, **10**, (4.2 g, 27 mmol), K_2CO_3 (4.1 g, 30 mmol), Cu powder (0.05 g), and Cu_2O (0.05 g), in 5 mL of 2-methoxyethanol was refluxed for 2 hours. The cooled reaction mixture was poured into 30 mL water. Charcoal was then added and the solution was filtrated through Celite. The crude product was obtained by acidification of the filtrate with diluted HCl at ambient temperature, and subsequent recrystallization from acetone/water (1:8). The crystals were dissolved in 100 mL 5 % aqueous Na_2CO_3. The solution was filtered through Celite and the product was precipitated by acidification to afford acid **11** (8.1 g, 95 %) as a light yellow powder. ^{1}H-NMR δ = 2.39 (s, 6H), 4.43 (s, 2H), 6.77 (dd, J = 7.1 Hz, 7.6 Hz, 1H), 7.02 (s, 1H), 7.22-7.50 (m, 8H), 8.06 (d, J = 8.0 Hz, 1H). ^{13}C-NMR δ = 21.7, 113.7, 114.4, 115.9, 117.5, 121.9, 122.1, 123.1, 125.2, 128.7, 129.3, 129.8, 133.9, 135.3, 138.5, 140.9, 143.0, 149.1. Anal. calcd. for $C_{21}H_{19}NO_2$: C, 79.50; H, 5.99; N, 4.42. Found: C, 79.10; H, 6.23; N, 4.32.

9-bromo-3-(3,5-dimethylphenyl)acridine, 12

Acid **11** (1.0 g, 3.15 mmol) was suspended in 11.0 g (38 mmol) of phosphorus oxybromide, and the mixture was heated to 120 °C for 2 hours. Excess phosphorus oxybromide was removed by distillation and the residual solution was poured into a 1:1 mixture of aqueous ammonium hydroxide:CH_2Cl_2. The CH_2Cl_2 solution was separated, dried, and dried in vacuo.

Purification of the orange residue by flash chromatography (100:100:1 hexanes:methylene chloride:triethylamine) gave **12** (0.5 g, 45 %) as a yellow powder. ^{1}H-NMR δ = 2.44 (s, 6H), 7.09 (s, 1H), 7.46 (s, 2H), 7.63 (ddd, *J* = 1.1 Hz, 6.6 Hz, 8.8 Hz, 1H), 8.28 (dd, *J* = 8.5 Hz, 6.9 Hz, 1H), 7.92 (dd, *J* = 1.6 Hz, 9.1 Hz, 1H), 8.22 (d, *J* = 8.8 Hz, 1H) 8.39-8.47 (m, 3H). ^{13}C-NMR δ = 22.0, 125.3, 125.5, 126.0, 126.7, 127.0, 127.2, 127.5, 127.8, 129.9, 130.2, 130.4, 135.4, 138.6, 139.3, 142.8, 149.2, 149.2. Anal. calcd. for $C_{21}H_{16}NBr$: C, 69.61; H, 4.42; N, 3.87. Found: C, 70.03; H, 4.30; N, 3.40.

3-(3,5-dimethylphenyl)-9-trimethylstannylacridine, 13

A solution of 9-bromo-3-(3,5-dimethylphenyl)acridine, **12**, (0.6 g, 1.6 mmol) in 10 ml anhydrous diethyl ether:THF (1:1) was cooled to -78°C. To the solution was added 1.6 M *n*-BuLi in hexanes (2.4 mmol, 1.5 mL) dropwise over a period of 15 min and then a 1.0 M solution of Me_3SnCl in hexanes (3 mL, 3 mmol). The reaction mixture was allowed to warm to room temperature, stirred for 18 hours and concentrated in vacuo. Purification of the orange residue by flash chromatography (100:30:1 hexanes:ethyl acetate:triethylamine) afforded **13** (0.65 g, 91 %) as a yellow solid. GC-MS revealed contamination of the product with 5-10% 3-(3,5-dimethylphenyl)acridine that could not be separated by chromatography. The stannane was therefore employed in the Stille cross-coupling with 1,8-dibromonaphthalene without further purification. ^{1}H-NMR δ = 0.70 (s, 9H), 2.44 (s, 6H), 7.08-7.10 (m, 1H), 7.49-7.56 (m, 3H), 7.76 (ddd, *J* = 1.4 Hz, 6.6 Hz, 8.8 Hz, 1H), 7.88 (dd, *J* = 1.9 Hz, 9.1 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 8.22 (d, *J* = 9.1 Hz, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 8.49 (m, 1H). ^{13}C-NMR δ = -4.2, 21.8, 125.3, 125.4, 125.5, 127.7, 129.6, 129.8, 130.1, 130.4, 130.8, 132.8, 133.5, 138.4, 139.8, 142.0, 148.2, 148.2, 156.4.

1,8-bis(3,3'-(3,5-dimethylphenyl)-9,9'-diacridyl)naphthalene, 15

A mixture of 1,8-dibromonaphthalene, **14**, (143 mg, 0.50 mmol), tetrakis(triphenylphosphine)palladium(0) (0.11 g, 0.10 mmol, 30 mol%), and CuO (80 mg, 1 mmol) in 5 mL DMF was stirred at 140°C. After 5 min, a solution of 3-(3,5-dimethylphenyl)-9-trimethylstannylacridine **13** (0.90 g, 2.0 mmol) in 2 mL of DMF was added in one portion. After 16 hours, the reaction mixture was quenched with 10% aqueous ammonium hydroxide, extracted with diethyl ether, dried over $MgSO_4$ and concentrated in vacuo. Purification of the orange residue by flash chromatography (100:5:1 hexanes:ethyl acetate:triethylamine) afforded **15** (100

mg, 30 %) as a yellow solid. The diastereoisomers were separated into 60% of the *anti*-isomer and 40 % of the *syn*-isomer. *anti*-Isomer: ^{1}H-NMR δ = 2.45 (s, 12H), 6.62-6.68 (m, 2H), 6.83-6.86 (m, 4H), 7.00-7.03 (m, 2H), 7.07 (s, 2H), 7.31-7.39 (m, 8H), 7.67 (d, *J* = 9.1 Hz, 2H), 7.73-7.78 (m, 2H), 7.91 (s, 2H). 8.31 (d, *J* = 8.2 Hz, 2H). ^{13}C-NMR δ = 22.3, 124.8, 125.4, 125.5, 125.6, 125.9, 126.2, 126.3, 126.6, 127.0, 129.3, 129.8, 130.1, 130.5, 131.2, 134.2, 134.6, 135.5, 139.0, 140.8, 141.9, 146.1, 147.5, 147.6. LC/APCI/MS: m/z = 691(M + H). Anal. calcd. for *anti*-$C_{52}H_{38}N_2$: C, 90.43; H, 5.55; N, 4.06. Found: C, 90.64; H, 5.30; N, 4.11. *syn*-Isomer: ^{1}H-NMR δ = 2.26 (s, 12H), 6.65-6.70 (m, 2H), 6.75-6.78 (m, 2H), 6.85-6.88 (m, 2H), 6.96-6.99 (m, 4H), 7.12 (s, 4H), 7.28-7.31 (m, 2H), 7.36-7.42 (m, 2H), 7.69-7.75 (m, 4H), 7.91 (d, *J* = 1.65 Hz, 2H), 8.27 (dd, *J* = 1.1 Hz, 8.36 Hz, 2H). ^{13}C-NMR δ = 22.0, 124.8, 125.3, 125.4, 125.5, 125.8, 126.1, 126.3, 126.4, 126.9, 129.4, 129.7, 130.1, 130.4, 131.1, 134.2, 134.7, 135.5, 138.8, 140.7, 142.1, 146.1, 147.4, 147.5. Anal. calcd. for *syn*-$C_{52}H_{38}N_2$: C, 90.43; H, 5.55; N, 4.06. Found: C, 90.70; H, 5.40; N, 4.36.

1,8-bis(3,3'-(3,5-dimethylphenyl)-9,9'-diacridyl)naphthalene N,N'-dioxide, 16

A solution of 1,8-bis(3,3'-(3,5-dimethylphenyl)-9,9'-diacridyl)naphthalene, **15**, (100 mg, 0.15 mmol) in 3 mL of THF was treated with perbenzoic acid (68 mg, 77% purity, 0.30 mmol) in 2 mL of THF at room temperature. The mixture was allowed to stir at room temperature for 5 hours and the solvent was removed by evaporation under reduced pressure. The residue was dissolved in methylene chloride and washed with 2N sodium hydroxide, dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (100:10 ethyl acetate:ethyl alcohol) afforded **1** (80 mg, 75 %) as a red solid. ^{1}H-NMR δ = 2.45 (s, 12H), 6.63-6.69 (m, 2H), 6.81 (d, *J* = 9.1 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 7.09-7.14 (m, 4H), 7.34-7.41 (m, 8H), 7.77 (dd, *J* = 7.2 Hz, 8.2 Hz, 2H), 8.32 (dd, *J* = 1.1 Hz, 8.2 Hz 2H), 8.47 (d, *J* = 9.1 Hz 2H). 8.69 (d, *J* = 1.7 Hz, 2H). ^{13}C-NMR δ = 22.3, 117.6, 120.5, 126.1, 126.5, 126.5, 126.6, 126.7, 126.3, 126.9, 127.5, 130.0, 130.7, 131.0, 132.2, 133.4, 134.1, 135.1, 135.9, 138.6, 138.6, 139.2, 140.2, 143.0. Anal. calcd. for $C_{52}H_{38}N_2O_2$: C, 86.43; H, 5.26; N, 3.88. Found: C, 86.40; H, 5.33; N, 3.76.

Incorporation by Reference

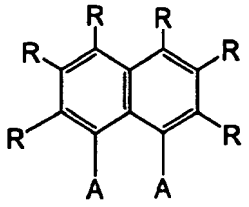
All of the patents and publications cited herein are hereby incorporated by reference.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

We claim:

1. A compound represented by formula I:



I

wherein

R represents independently for each occurrence H, alkyl, aryl, aralkyl, or alkenyl; and

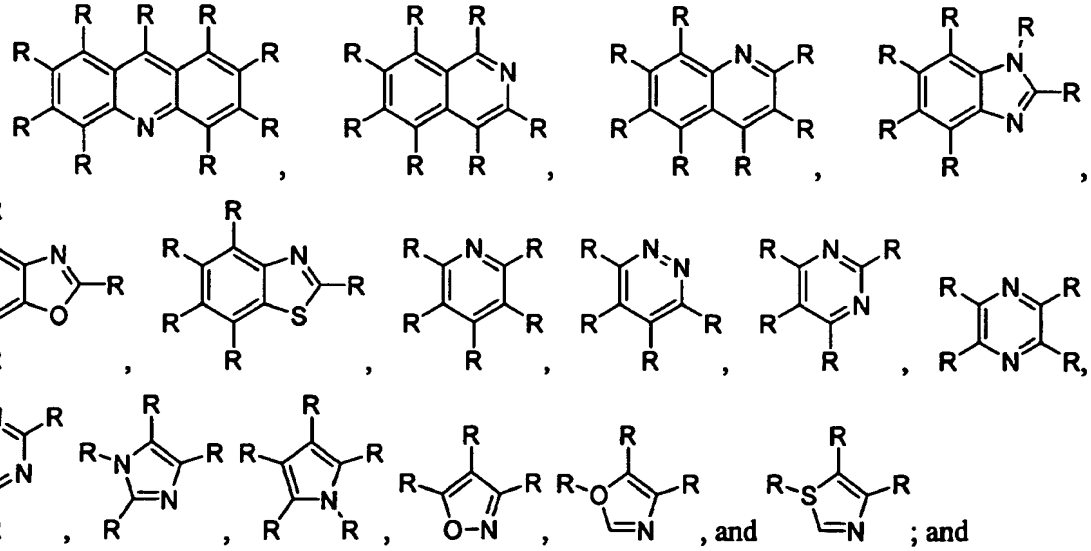
A represents independently for each occurrence aryl or heteroaryl.

2. The compound of claim 1, wherein R represents independently for each occurrence H or alkyl.

3. The compound of claim 1, wherein A is heteroaryl.

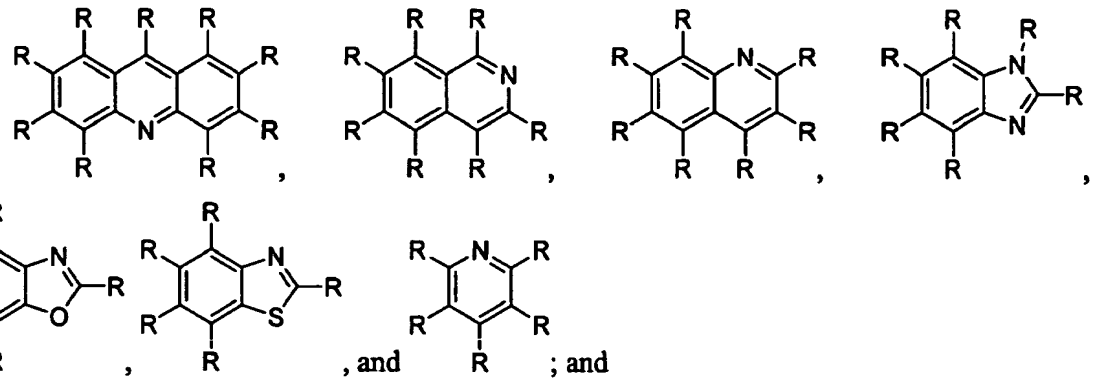
4. The compound of claim 1, wherein A is heteroaryl, and R represents independently for each occurrence H or alkyl.

5. The compound of claim 1, wherein A is selected from the group consisting of:



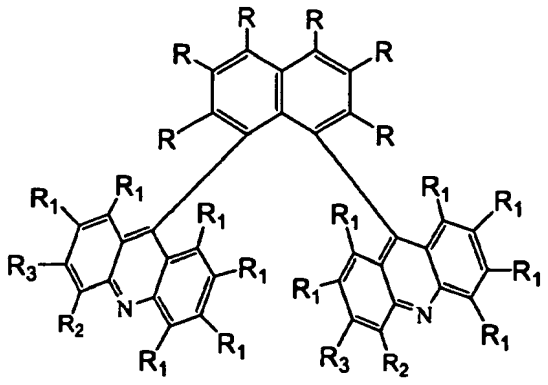
R represents independently for each occurrence H, alkyl, aryl, or a bond to the nathphyl ring of the compound represented by formula I.

6. The compound of claim 1, wherein A is selected from the group consisting of:



R represents independently for each occurrence H, alkyl, aryl, or a bond to the nathphyl ring of the compound represented by formula **I**.

7. A compound represented by formula **II**:



II

wherein

R, R_1, R_2, and R_3 represent independently for each occurrence H, alkyl, aryl, aralkyl, or alkenyl.

8. The compound of claim 7, wherein R represents independently for each occurrence H or alkyl.

9. The compound of claim 7, wherein R represents independently for each occurrence H.

10. The compound of claim 7, wherein R_1 represents independently for each occurrence H or alkyl.

11. The compound of claim 7, wherein R_1 represents independently for each occurrence H.

12. The compound of claim 7, wherein R_2 represents independently for each occurrence H, alkyl, or aryl.

13. The compound of claim 7, wherein R_2 represents independently for each occurrence alkyl.

14. The compound of claim 7, wherein R_2 represents independently for each occurrence methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, or pentyl.

15. The compound of claim 7, wherein R_2 represents independently for each occurrence methyl or isopropyl.

16. The compound of claim 7, wherein R_3 represents independently for each occurrence H, alkyl, or aryl.

17. The compound of claim 7, wherein R_3 represents independently for each occurrence aryl.

18. The compound of claim 7, wherein R_3 represents independently for each occurrence an optionally subsituted phenyl group.

19. The compound of claim 7, wherein R_3 represents independently for each occurrence 3,5-dimethylphenyl.

20. The compound of claim 7, wherein R is H, R_1 is H, R_3 is H, and R_2 is alkyl.

21. The compound of claim 7, wherein R is H, R_1 is H, R_3 is H, and R_2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, or pentyl.

22. The compound of claim 7, wherein R is H, R_1 is H, R_3 is H, and R_2 is methyl.

23. The compound of claim 7, wherein R is H, R_1 is H, R_3 is H, and R_2 is isopropyl.

24. The compound of claim 7, wherein R is H, R_1 is H, R_2 is H, and R_3 represents independently for each occurrence aryl.

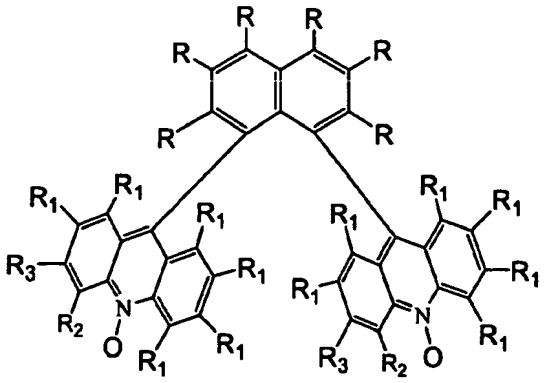
25. The compound of claim 7, wherein R is H, R_1 is H, R_2 is H, and R_3 represents independently for each occurrence an optionally substituted phenyl group.

26. The compound of claim 7, wherein R is H, R_1 is H, R_2 is H, and R_3 is 3,5-dimethylphenyl.

27. The compound of claim 7, wherein said compound is a chiral.

28. The compound of claim 7, wherein said compound is a single diastereomer.

29. A compound represented by formula **III**:



III

wherein

R, R_1, R_2, and R_3 represent independently for each occurrence H, alkyl, aryl, aralkyl, or alkenyl.

30. The compound of claim 29, wherein R represents independently for each occurrence H or alkyl.

31. The compound of claim 29, wherein R represents independently for each occurrence H.

32. The compound of claim 29, wherein R_1 represents independently for each occurrence H or alkyl.

33. The compound of claim 29, wherein R_1 represents independently for each occurrence H.

34. The compound of claim 29, wherein R_2 represents independently for each occurrence H, alkyl, or aryl.

35. The compound of claim 29, wherein R_2 represents independently for each occurrence alkyl.

36. The compound of claim 29, wherein R_2 represents independently for each occurrence methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, or pentyl.

37. The compound of claim 29, wherein R_3 represents independently for each occurrence H, alkyl, or aryl.

38. The compound of claim 29, wherein R_3 represents independently for each occurrence aryl.

39. The compound of claim 29, wherein R_3 represents independently for each occurrence an optionally subsituted phenyl group.

40. The compound of claim 29, wherein R_3 represents independently for each occurrence 3,5-dimethylphenyl.

41. The compound of claim 29, wherein R is H, R_1 is H, R_3 is H, and R_2 is alkyl.

42. The compound of claim 29, wherein R is H, R_1 is H, R_3 is H, and R_2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, or pentyl.

43. The compound of claim 29, wherein R is H, R_1 is H, R_3 is H, and R_2 is methyl.

44. The compound of claim 29, wherein R is H, R_1 is H, R_3 is H, and R_2 is isopropyl.

45. The compound of claim 29, wherein R is H, R_1 is H, R_2 is H, and R_3 represents independently for each occurrence aryl.

46. The compound of claim 29, wherein R is H, R_1 is H, R_2 is H, and R_3 represents independently for each occurrence an optionally substituted phenyl group.

47. The compound of claim 29, wherein R is H, R_1 is H, R_2 is H, and R_3 is 3,5-dimethylphenyl.

48. The compound of claim 29, wherein said compound is a single enantiomer.

49. A method of detecting an analyte, comprising the step of:

contacting an analyte with a compound of claim 7, and comparing the fluorescence of said compound of claim 7 in the presence of said analyte to the fluoresence of said compound of claim 7 in the absence of said analyte.

50. The method of claim 49, wherein the analyte is a cation.

51. The method of claim 49, wherein the analyte is a alkali, alkaline earth, or transition metal ion.

52. The method of claim 49, wherein the analyte is a alkali or alkaline earth metal ion.

53. The method of claim 49, wherein the analyte is a lithium, sodium, potassium, magnesium, calcium, or strontium metal ion.

54. The method of claim 49, wherein the analyte is a sodium, potassium, or calcium metal ion.

55. The method of claim 49, wherein the analyte is a transition metal ion.

56. The method of claim 49, wherein the analyte is a copper, iron, nickel, manganese, cobalt, chromium, vanadium, titanium, zirconium, rhodium, palladium, silver, cadmium, mercury, gold, platinum, or hafnium ion.

57. The method of claim 49, wherein the analyte is a copper, iron, nickel, or manganese ion.

58. The method of claim 49, wherein the analyte is a copper ion.

59. The method of claim 49, wherein the analyte is a Cu^{2+}.

60. A method of detecting an analyte, comprising the step of:

contacting an analyte with a compound of claim 29, and comparing the fluorescence of said compound of claim 29 in the presence of said analyte to the fluoresence of said compound of claim 29 in the absence of said analyte.

61. The method of claim 60, wherein the analyte is a compound that comprises a hydrogen atom capable of participating in a hydrogen bond.

62. The method of claim 60, wherein the analyte is a compound that comprises a hydroxyl, carboxylic acid, amine, amide, thiol, or percarboxylic acid functional group.

63. The method of claim 60, wherein the analyte is a compound that comprises a hydroxyl, carboxylic acid, or amine functional group.

64. The method of claim 60, wherein the analyte is a compound that comprises a hydroxyl functional group.

65. The method of claim 60, wherein the analyte is a compound that comprises a carboxylic acid functional group.

66. The method of claim 60, wherein the analyte is a chiral compound that comprises a hydrogen atom capable of participating in a hydrogen bond.

67. The method of claim 60, wherein the analyte is a chiral compound that comprises a hydroxyl, carboxylic acid, amine, amide, thiol, or percarboxylic acid functional group.

68. The method of claim 60, wherein the analyte is a chiral compound that comprises a hydroxyl, carboxylic acid, or amine functional group.

69. The method of claim 60, wherein the analyte is a chiral compound that comprises a hydroxyl functional group.

70. The method of claim 60, wherein the analyte is a chiral compound that comprises a carboxylic acid functional group.

Figure 1

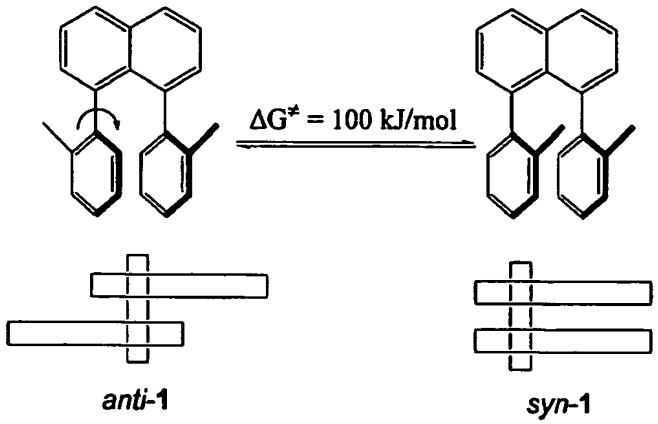


Figure 2

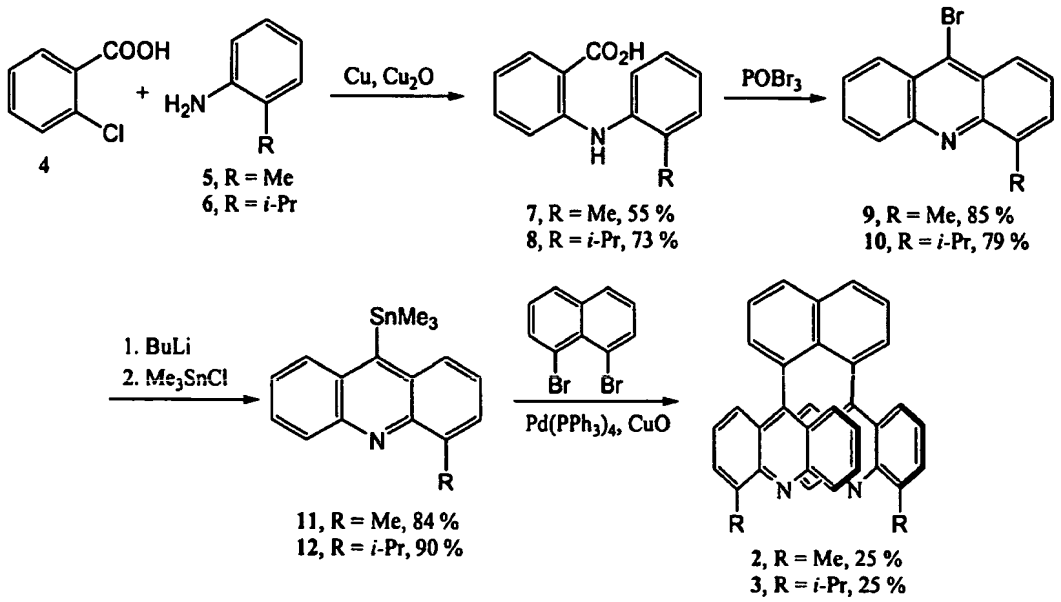

COOH
Cl
4
+ H2N
R
5, R = Me
6, R = i-Pr
Cu, Cu2O
CO2H
N
H
R
7, R = Me, 55 %
8, R = i-Pr, 73 %
POBr3
Br
N
R
9, R = Me, 85 %
10, R = i-Pr, 79 %
1. BuLi
2. Me3SnCl
SnMe3
N
R
11, R = Me, 84 %
12, R = i-Pr, 90 %
Br Br
Pd(PPh3)4, CuO
N
N
R
R
2, R = Me, 25 %
3, R = i-Pr, 25 %

Figure 3

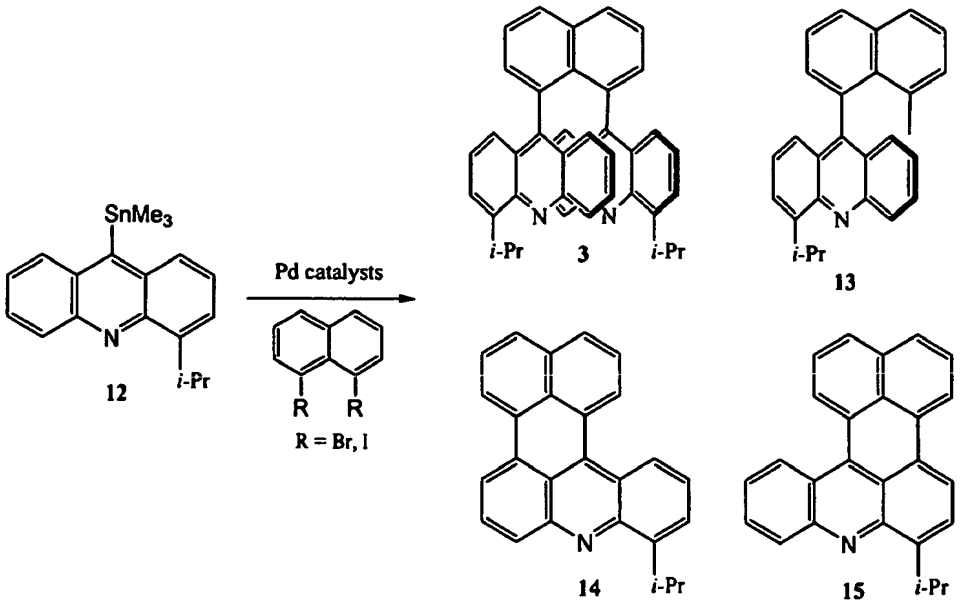

SnMe3
N
i-Pr
12
Pd catalysts
R R
R = Br, I
N
N
i-Pr
3
i-Pr
N
i-Pr
13
N
i-Pr
14
N
i-Pr
15

Figure 4

entry		stannane	Catalyst (mol%)	additives	yield of major product (%)
1	R = I	**12**	$Pd(PPh_3)_4$ (10)[a]	/	**14** + **15** (17)
2	R = I	**12**	$Pd(PPh_3)_4$ (10)[a]	Cy_2NMe	**14** + **15** (17)
3	R = Br	**12**	$Pd(PPh_3)_4$ (10)[b]	CuO	**3** (5)
4	R = Br	**12**	$Pd(PPh_3)_4$ (10)[c]	CuO	**3** (5)
5	R = Br	**12**	$Pd(PPh_3)_4$ (10)[a]	CuO	**3** (10)
6	R = Br	**12**	$Pd(PPh_3)_4$ (20)[a]	CuO	**3** (18)
7	R = Br	**12**	$Pd(PPh_3)_4$ (30)[a]	CuO	**3** (25)
8	R = Br	**12**	$Pd(PPh_3)_4$ (40)[a]	CuO	**3** (25)
9	R = Br	**12**	$Pd(PPh_3)_4$ (50)[a]	CuO	**3** (25)
10	R = Br	**11**	$Pd(PPh_3)_4$ (30)[a]	CuO	**2** (25)

Figure 5

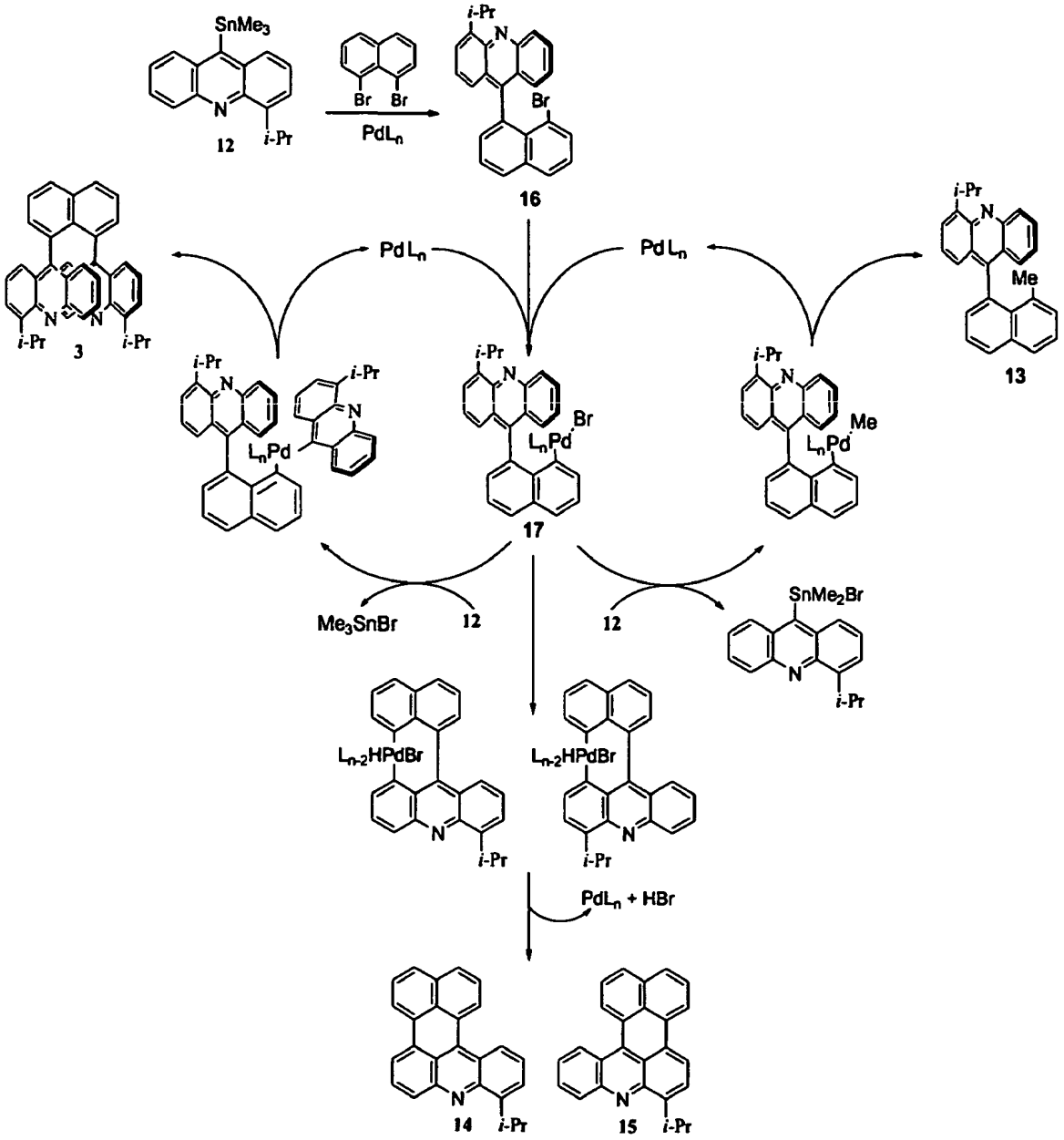

SnMe3
12
i-Pr
Br Br
PdLn
16
Br
i-Pr
N
PdLn
PdLn
3
i-Pr
N
N
i-Pr
i-Pr
i-Pr
N
LnPd
i-Pr
N
17
LnPd
Br
LnPd
Me
13
i-Pr
N
Me
Me3SnBr
12
12
SnMe2Br
N
i-Pr
Ln-2HPdBr
N
i-Pr
Ln-2HPdBr
N
i-Pr
PdLn + HBr
N
14
i-Pr
N
15
i-Pr

Figure 6

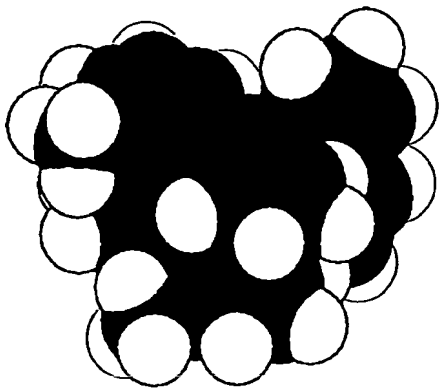


Figure 7

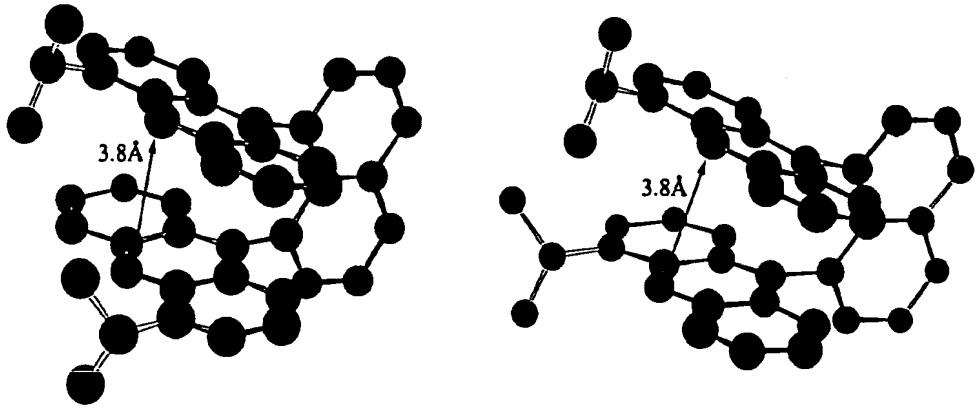


Figure 8

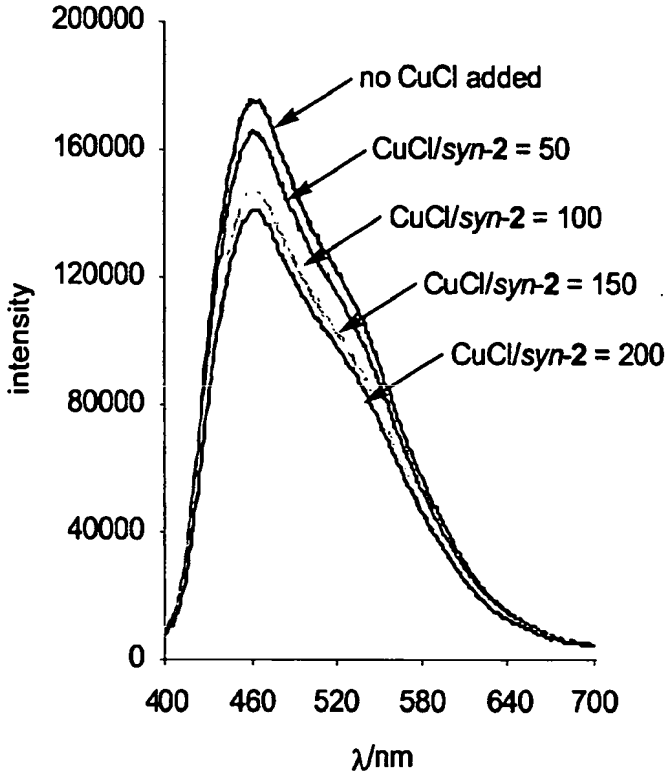

200000
160000
120000
80000
40000
0
intensity
400
460
520
580
640
700
λ/nm
no CuCl added
CuCl/syn-2 = 50
CuCl/syn-2 = 100
CuCl/syn-2 = 150
CuCl/syn-2 = 200

Figure 9

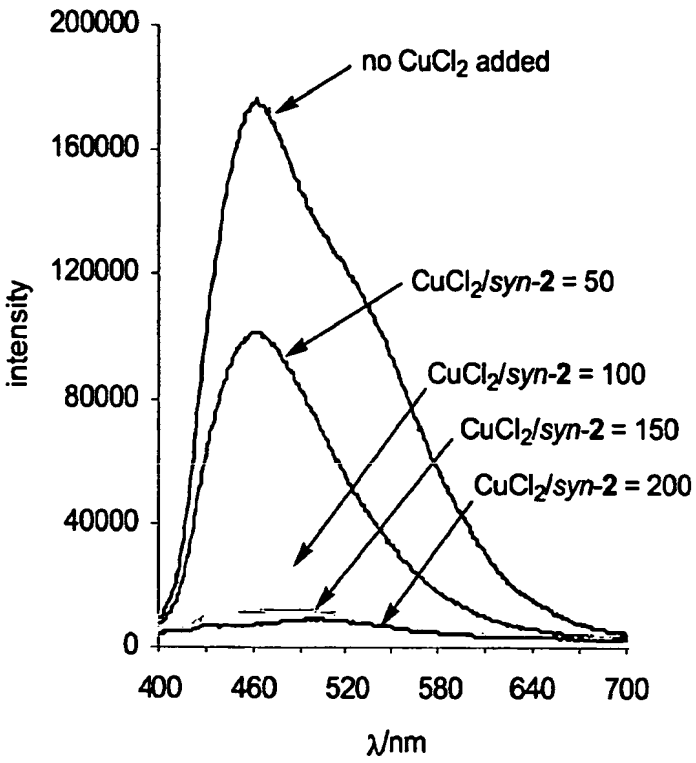

200000
160000
120000
80000
40000
0
intensity
400
460
520
580
640
700
λ/nm
no CuCl2 added
CuCl2/syn-2 = 50
CuCl2/syn-2 = 100
CuCl2/syn-2 = 150
CuCl2/syn-2 = 200

Figure 10

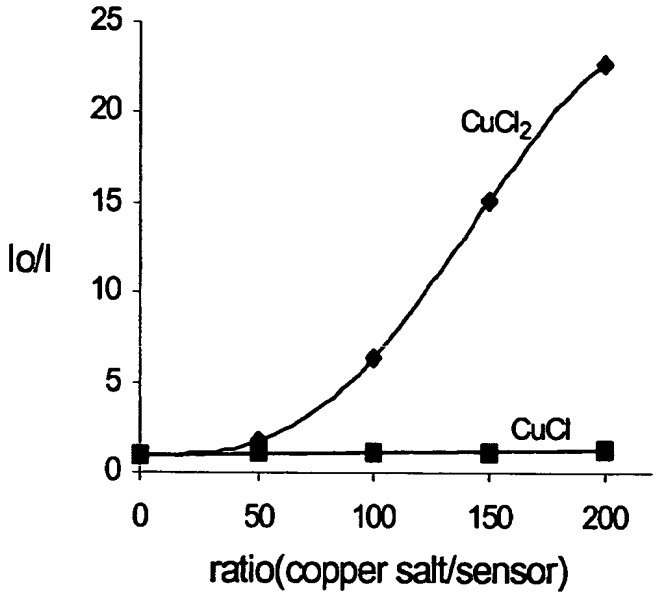

25
20
15
10
5
0
Io/I
CuCl2
CuCl
0
50
100
150
200
ratio(copper salt/sensor)

Figure 11

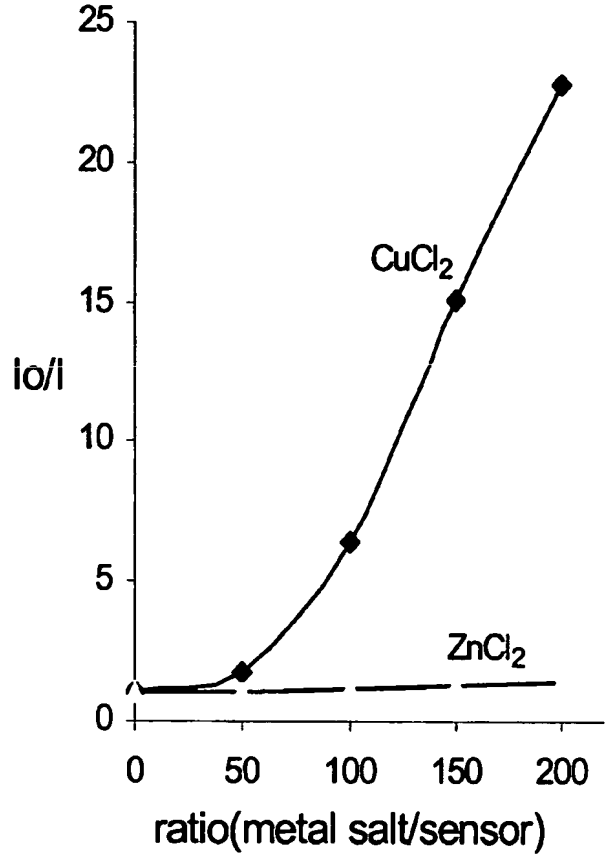

25
20
15
10
5
0
Io/I
CuCl2
ZnCl2
0
50
100
150
200
ratio(metal salt/sensor)

Figure 12

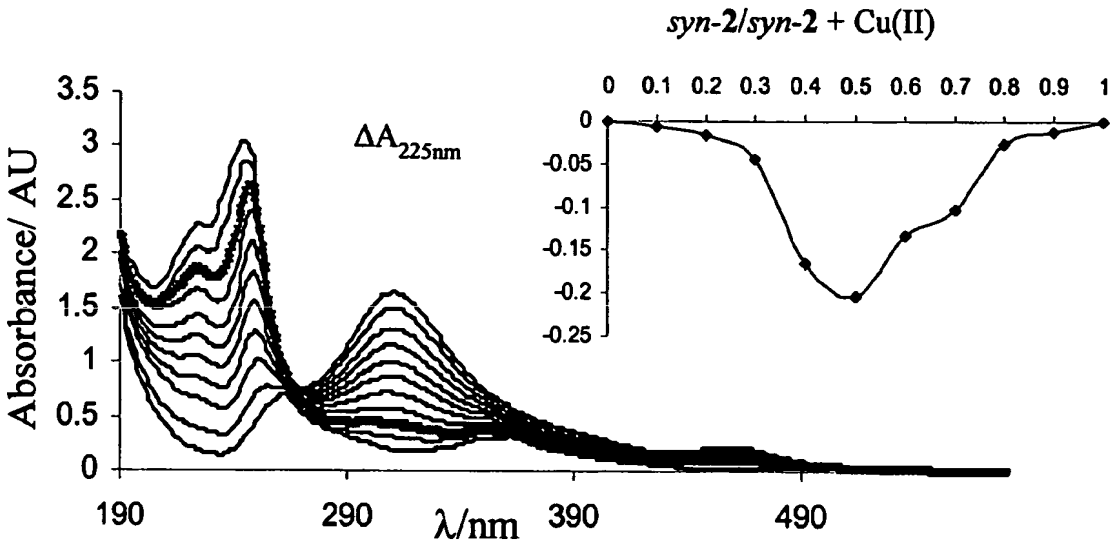

syn-2/syn-2 + Cu(II)
ΔA225nm
Absorbance/ AU
λ/nm
3.5
3
2.5
2
1.5
1
0.5
0
190
290
390
490
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1
0
-0.05
-0.1
-0.15
-0.2
-0.25

Figure 13

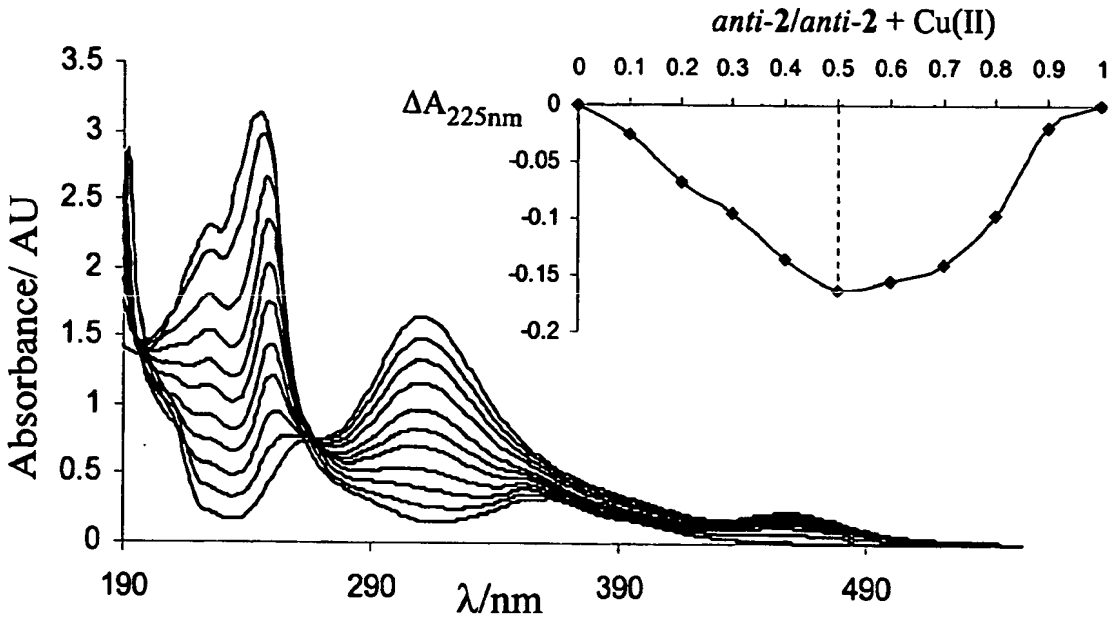

anti-2/anti-2 + Cu(II)
ΔA225nm
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1
0
-0.05
-0.1
-0.15
-0.2
Absorbance/ AU
3.5
3
2.5
2
1.5
1
0.5
0
190
290
λ/nm
390
490

Figure 14

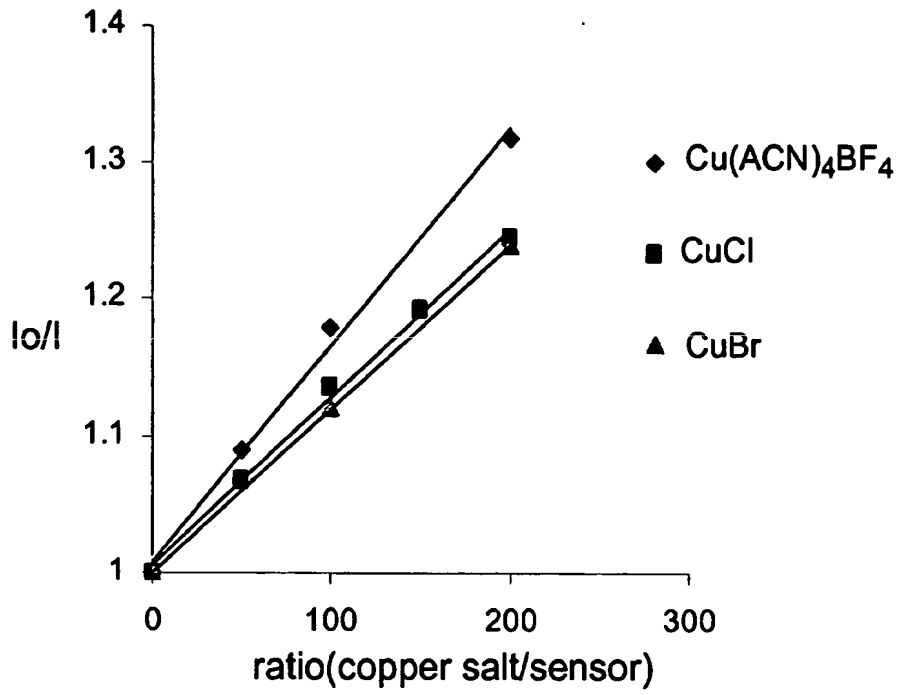

1.4
1.3
1.2
1.1
1
Io/I
0
100
200
300
ratio(copper salt/sensor)
Cu(ACN)4BF4
CuCl
CuBr

Figure 15

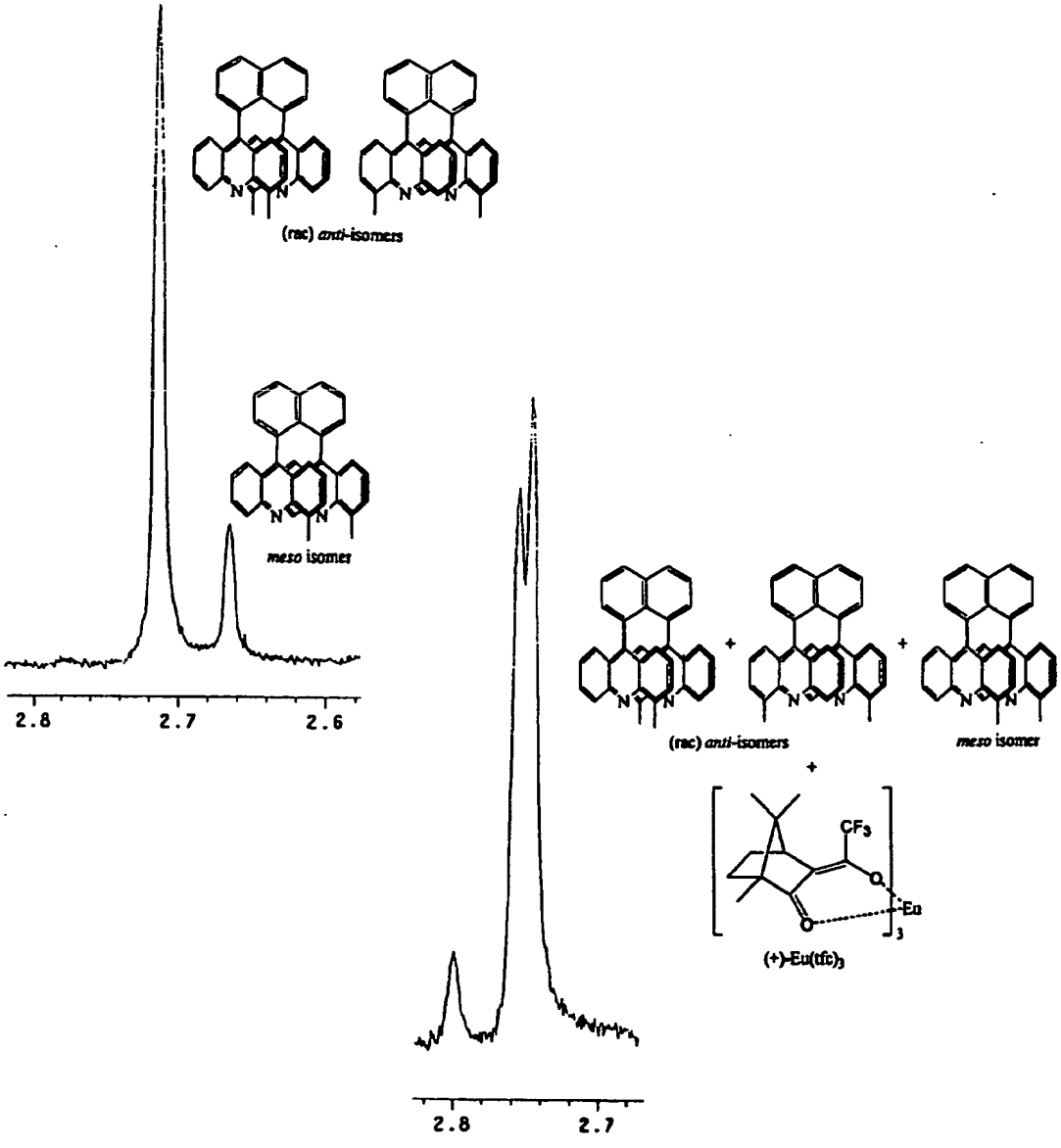

(rac) anti-isomers
meso isomer
2.8
2.7
2.6
(rac) anti-isomers
meso isomer
CF3
O
Eu
3
(+)-Eu(tfc)3
2.8
2.7

Figure 16

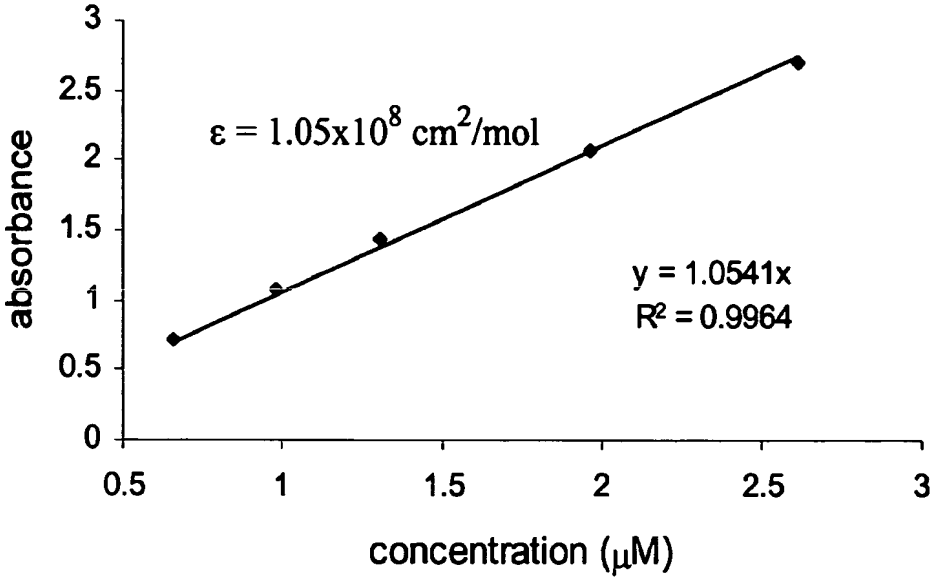

absorbance
concentration (μM)
ε = 1.05x10^8 cm^2/mol
y = 1.0541x
R² = 0.9964
0
0.5
1
1.5
2
2.5
3

Figure 17

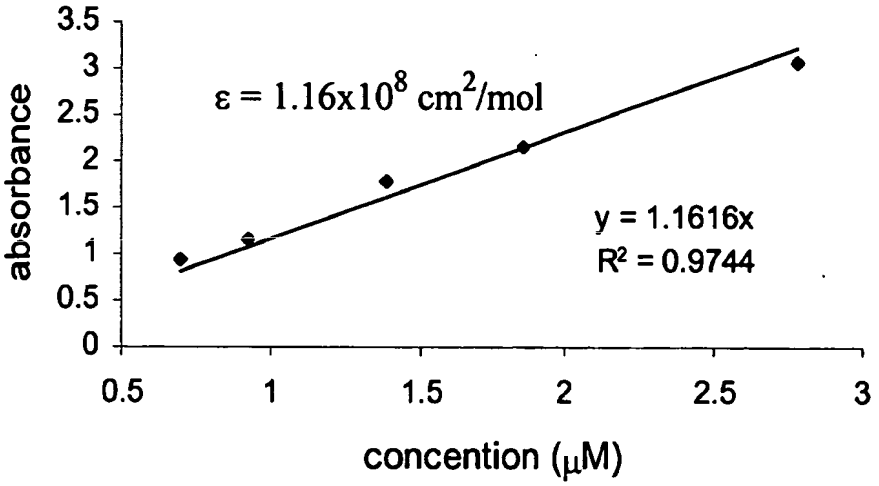

3.5
3
2.5
2
1.5
1
0.5
0
absorbance
ε = 1.16x10^8 cm^2/mol
y = 1.1616x
R² = 0.9744
0.5
1
1.5
2
2.5
3
concention (μM)

Figure 18

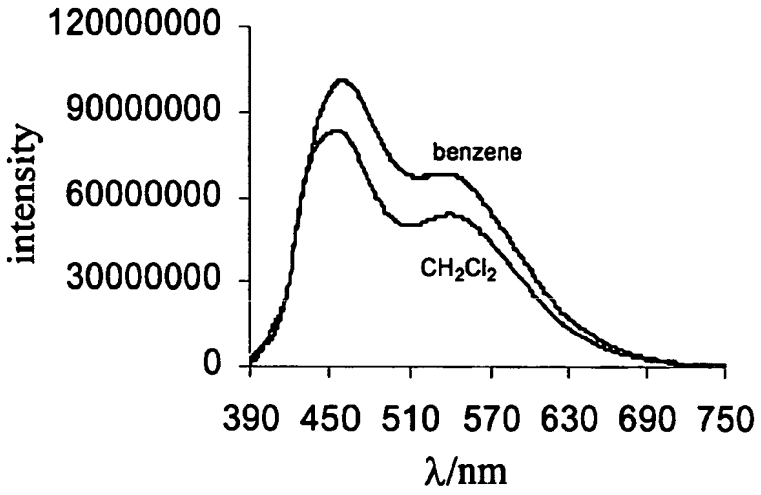
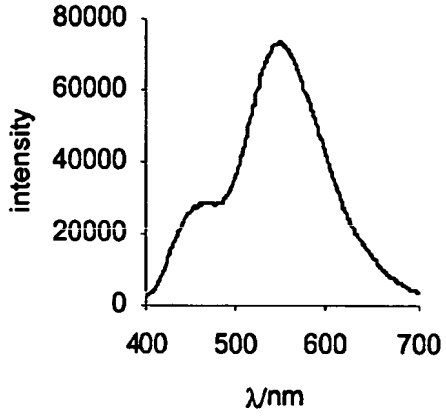

120000000
90000000
60000000
30000000
0
intensity
benzene
CH_2Cl_2
390 450 510 570 630 690 750
λ/nm

Figure 19


80000
60000
40000
20000
0
intensity
400
500
600
700
λ/nm

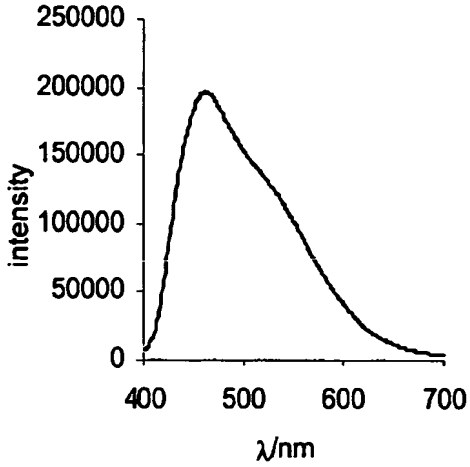

250000
200000
150000
100000
50000
0
intensity
400
500
600
700
λ/nm

Figure 20

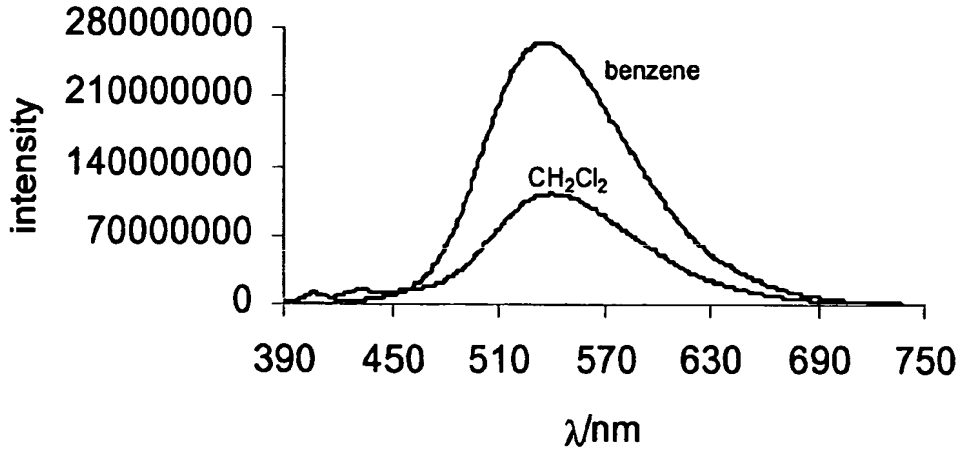
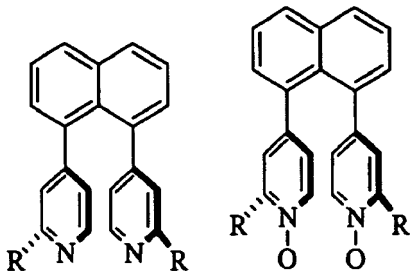

280000000
210000000
140000000
70000000
0
intensity
benzene
CH_2Cl_2
390
450
510
570
630
690
750
λ/nm

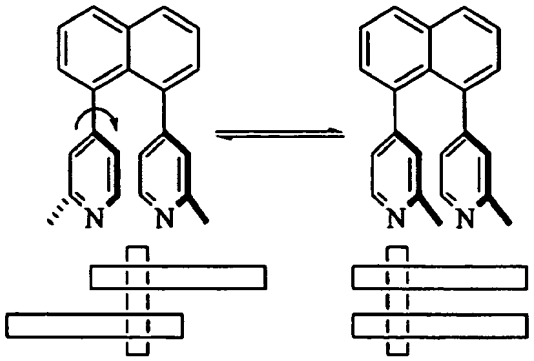
Figure 21



18: R=Me
19: R=Ph

20: R=Me
21: R=Ph

Figure 22



anti-**18** *syn*-**18**

Figure 23

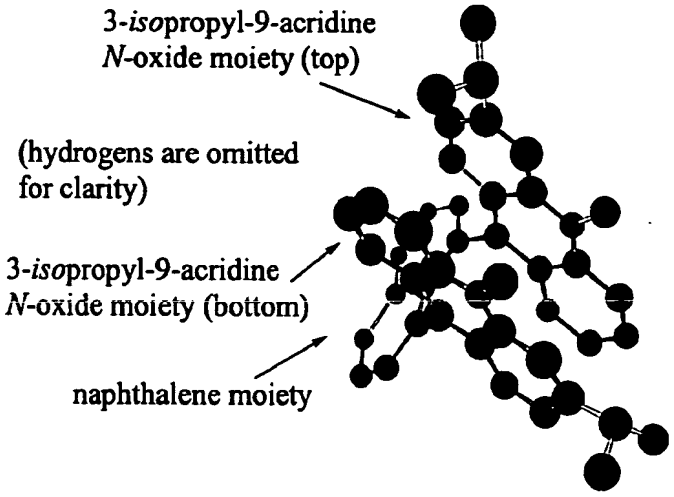

3-*iso*propyl-9-acridine
N-oxide moiety (top)
(hydrogens are omitted
for clarity)
3-*iso*propyl-9-acridine
N-oxide moiety (bottom)
naphthalene moiety

Figure 24

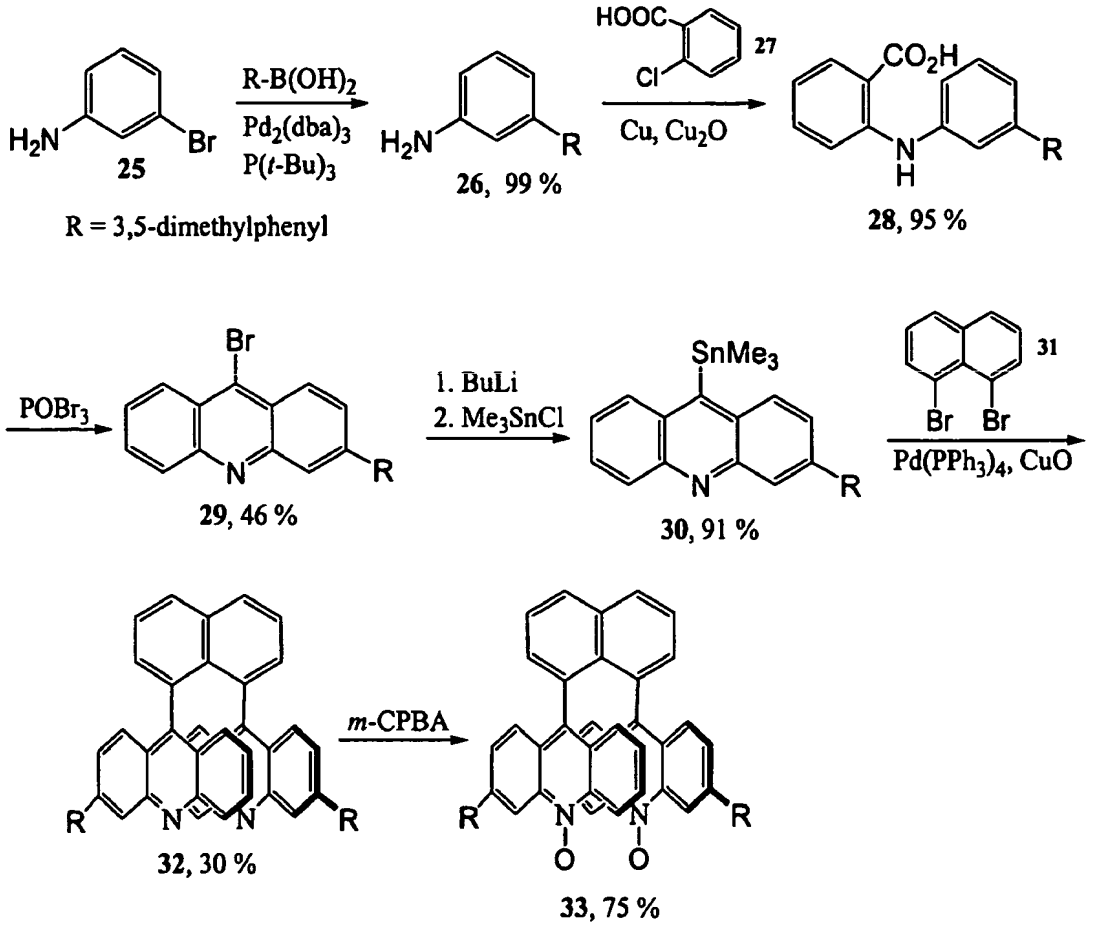

R-B(OH)2
Pd2(dba)3
P(t-Bu)3
25
R = 3,5-dimethylphenyl
26, 99 %
HOOC
Cl
27
Cu, Cu2O
CO2H
N
H
28, 95 %
POBr3
29, 46 %
1. BuLi
2. Me3SnCl
SnMe3
30, 91 %
31
Br Br
Pd(PPh3)4, CuO
m-CPBA
32, 30 %
33, 75 %

Figure 25

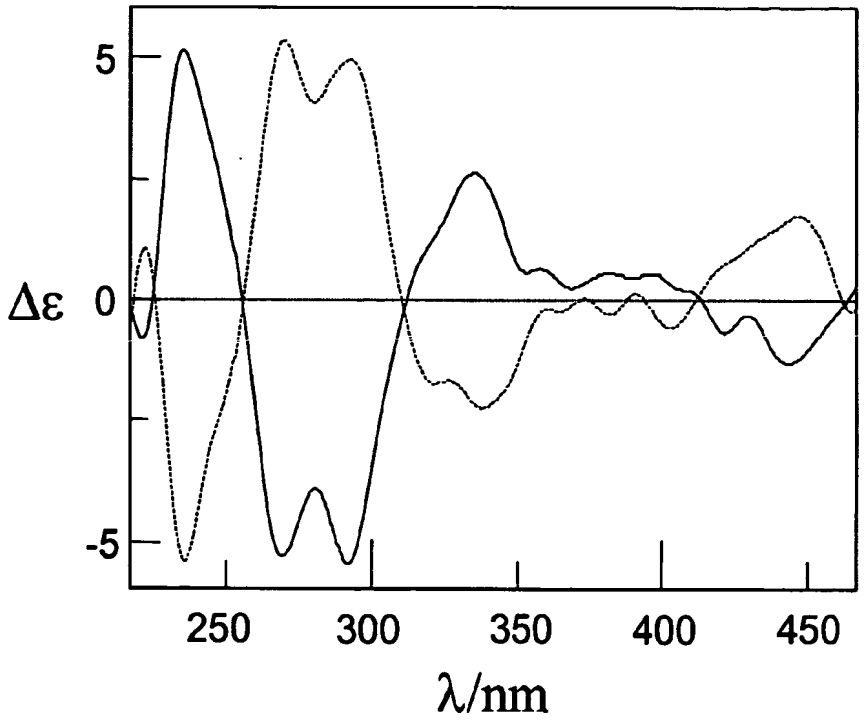
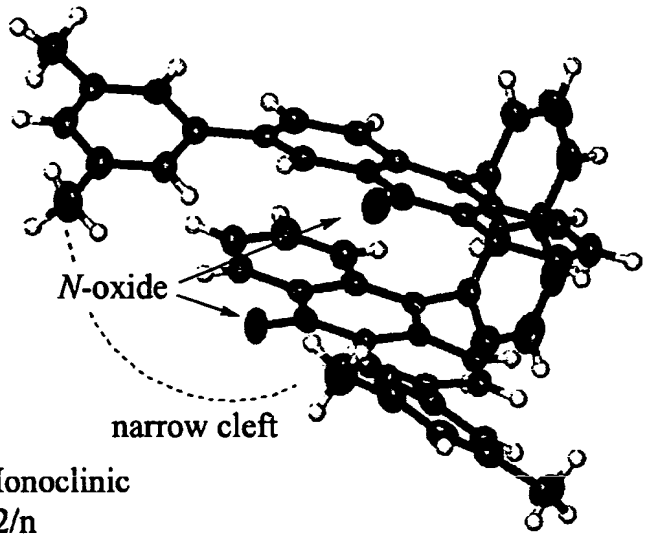


Figure 26



Monoclinic
P2/n
distance between *N*-oxides: 4.32 Å

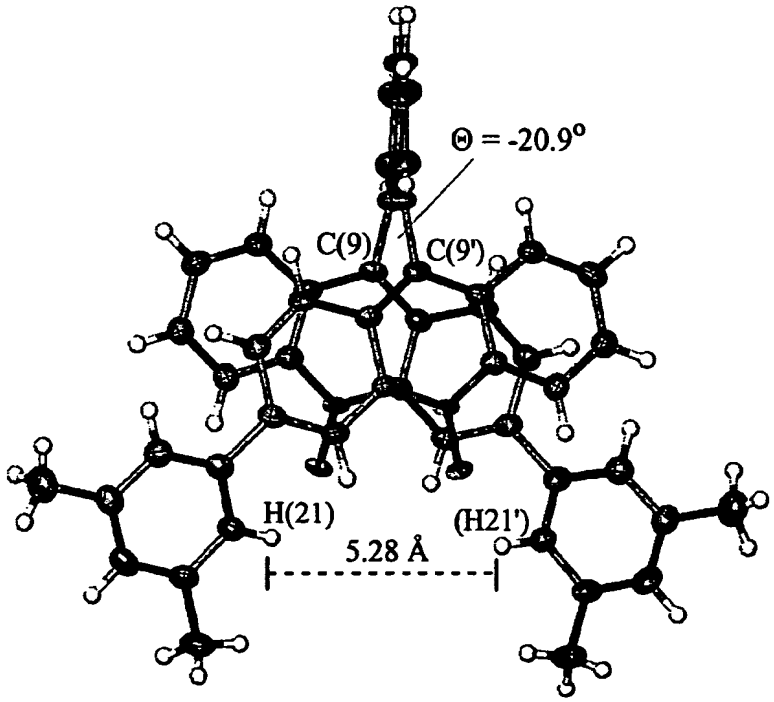
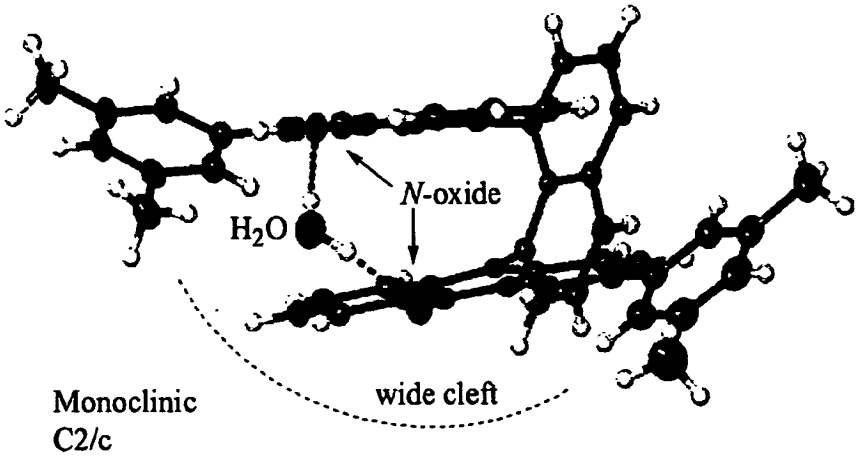


Figure 27



Monoclinic
C2/c
distance between *N*-oxides: 4.30 Å
hydrogen bond distance: 1.99 Å

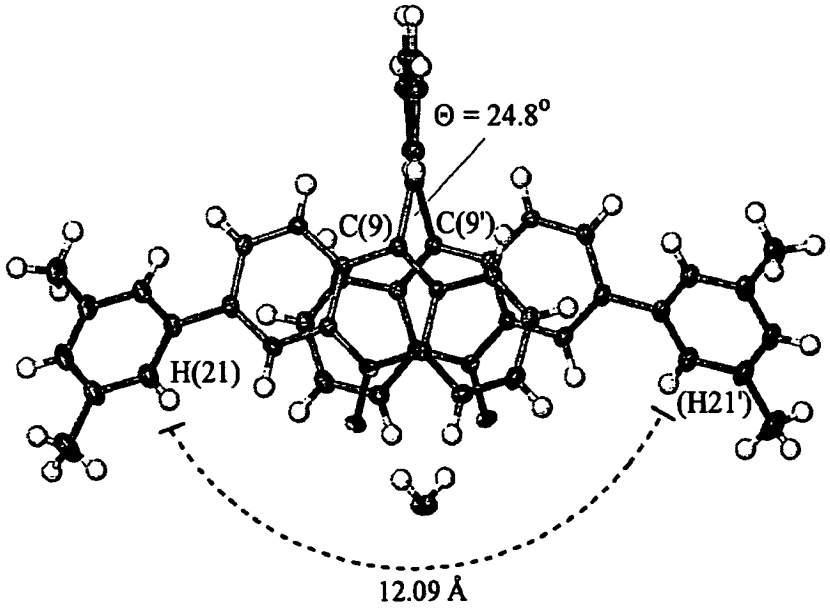


Figure 28

complex:	33-H_2O-CH_3CN	33-CH_2Cl_2
empirical formula	C28 H23 N2 O1.50	C27 H21 Cl2 N O
formula weight	411.48	446.35
temperature	186(2) K	183(2) K
wavelength	0.71073 Å	0.71073 Å
crystal system	Monoclinic	Monoclinic
space group	C2/c	P2/n
unit cell dimensions	a = 24.551(2) Å b = 13.3883(12) Å c = 13.7187(12) Å α= 90° β= 107.204(2)° γ = 90°	a = 13.839(2) Å b = 11.2871(18) Å c = 15.055(3) Å γ = 90° α= 90° β= 113.991(3)° γ = 90°
distance O-O	4.32 Å	4.30 Å
distance N-N	3.84 Å	3.82 Å
distance C(9)-C(9')	2.87 Å	2.91 Å
distance H(21)-H(21')	12.09 Å	5.28 Å
torsion Θ between acridyl rings	24.8°	-20.9°
Volume	4307.5(7) $Å^3$	2148.4(6) $Å^3$
Z	8	4
density (calculated)	1.269 Mg/m^3	1.380 Mg/m^3
Absorption coefficient	0.079 mm^{-1}	0.322 mm^{-1}
F(000)	1736	928
crystal size	0.95 x 0.46 x 0.46 mm^3	0.50 x 0.30 x 0.20 mm^3
theta range for data collection	1.74 to 27.00°.	1.69 to 25.00°.
index ranges	-31<=h<=31, -16<=k<=17, -17<=l<=17	-16<=h<=15, -13<=k<=10, -17<=l<=17
Reflections collected	18167	10895
independent reflections	4690 [R(int) = 0.0368]	3798 [R(int) = 0.0654]
completeness to theta = 27.00°	99.8 %	99.9 %
max. and min. transmission	0.9647 and 0.9289	0.9383 and 0.8554
refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
data / restraints / parameters	4690 / 0 / 292	3798 / 0 / 283
goodness-of-fit on F^2	1.090	0.875
final R indices [I>2sigma(I)]	R1 = 0.0568, wR2 = 0.1498	R1 = 0.0539, wR2 = 0.1284
largest diff. peak and hole	0.610 and -0.467 $e.Å^{-3}$	0.279 and -0.345 $e.Å^{-3}$

Figure 29

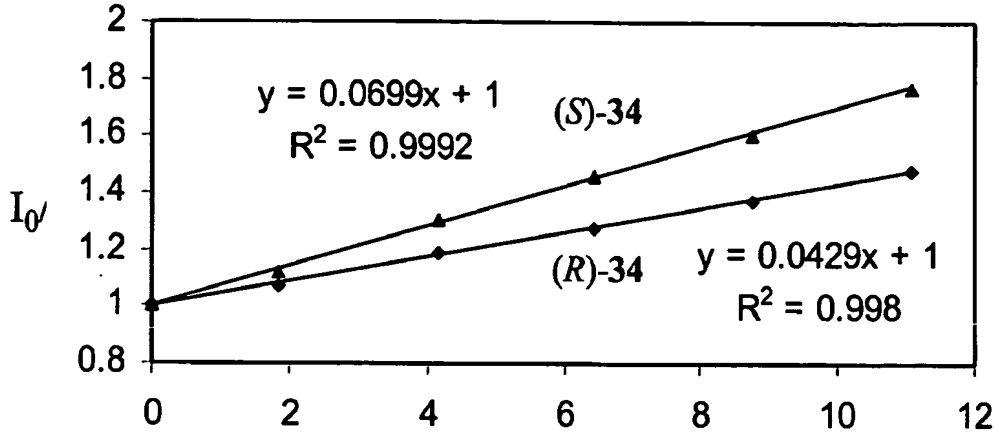

2
1.8
1.6
1.4
1.2
1
0.8
$I_0/$
y = 0.0699x + 1
R^2 = 0.9992
(S)-34
(R)-34
y = 0.0429x + 1
R^2 = 0.998
0
2
4
6
8
10
12

Figure 30

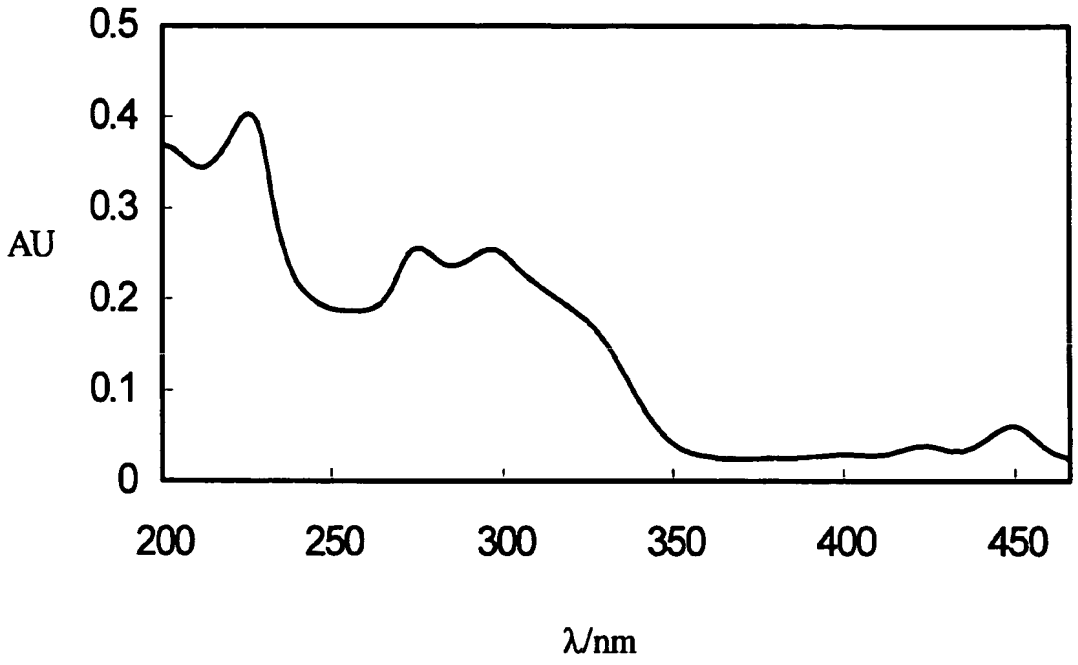


Figure 31

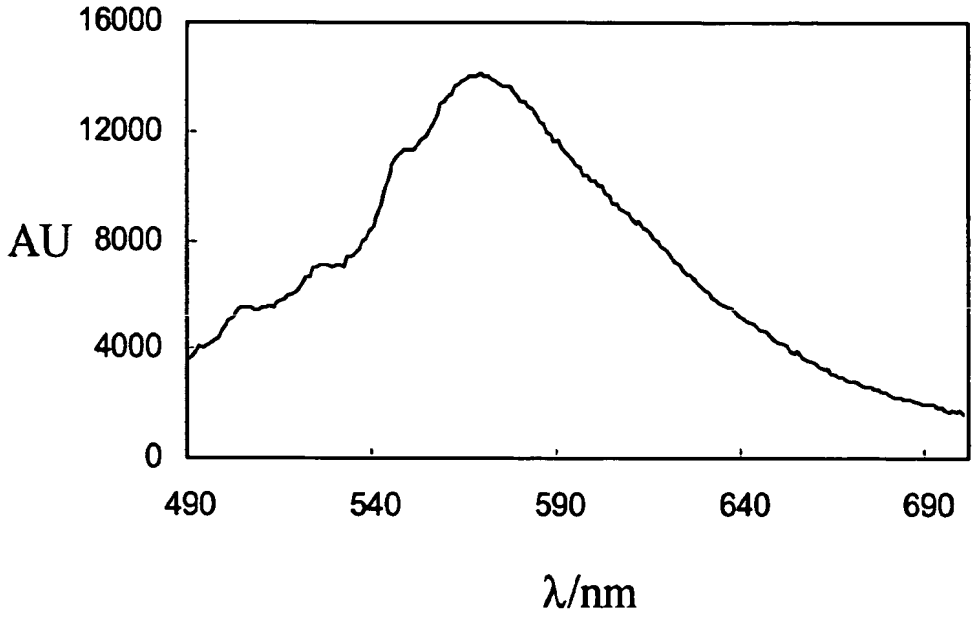


Figure 32

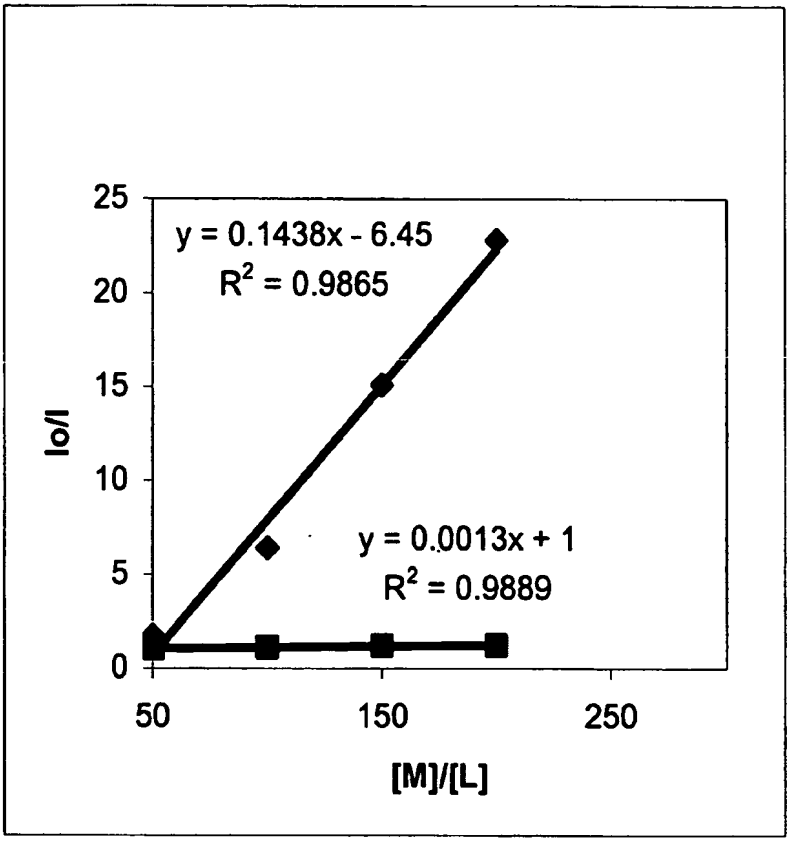

y = 0.1438x - 6.45
R2 = 0.9865
y = 0.0013x + 1
R2 = 0.9889
Io/I
[M]/[L]
0
5
10
15
20
25
50
150
250

Figure 33

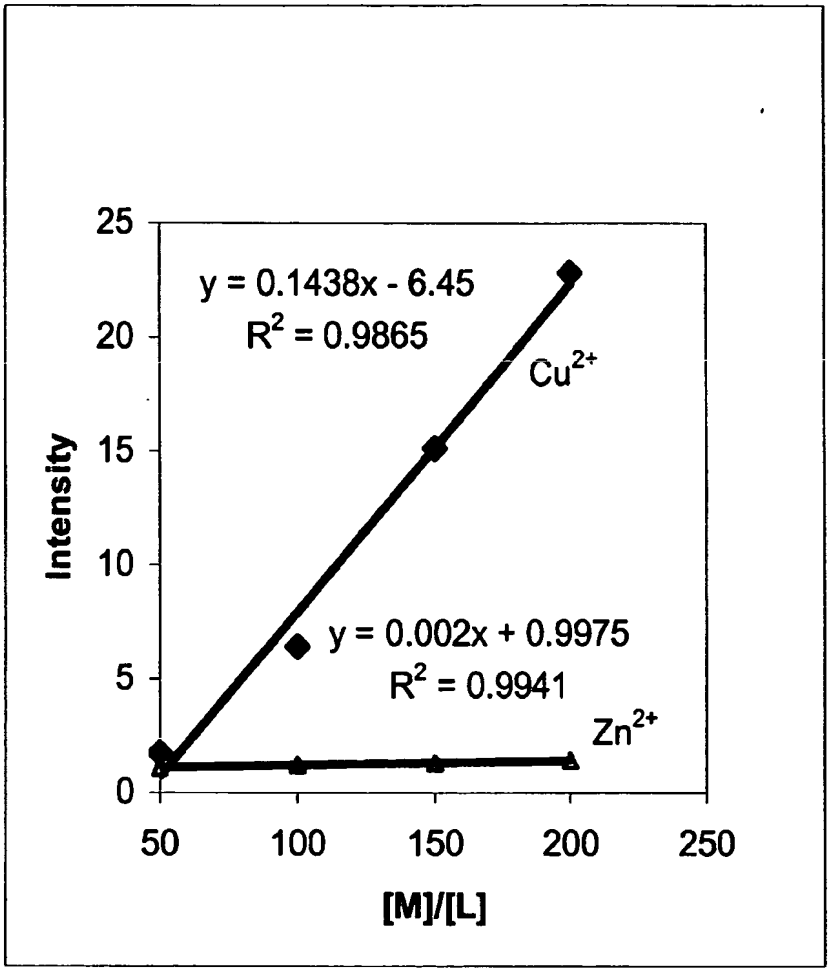

25
20
15
10
5
0
Intensity
y = 0.1438x - 6.45
R2 = 0.9865
Cu2+
y = 0.002x + 0.9975
R2 = 0.9941
Zn2+
50
100
150
200
250
[M]/[L]

Figure 34

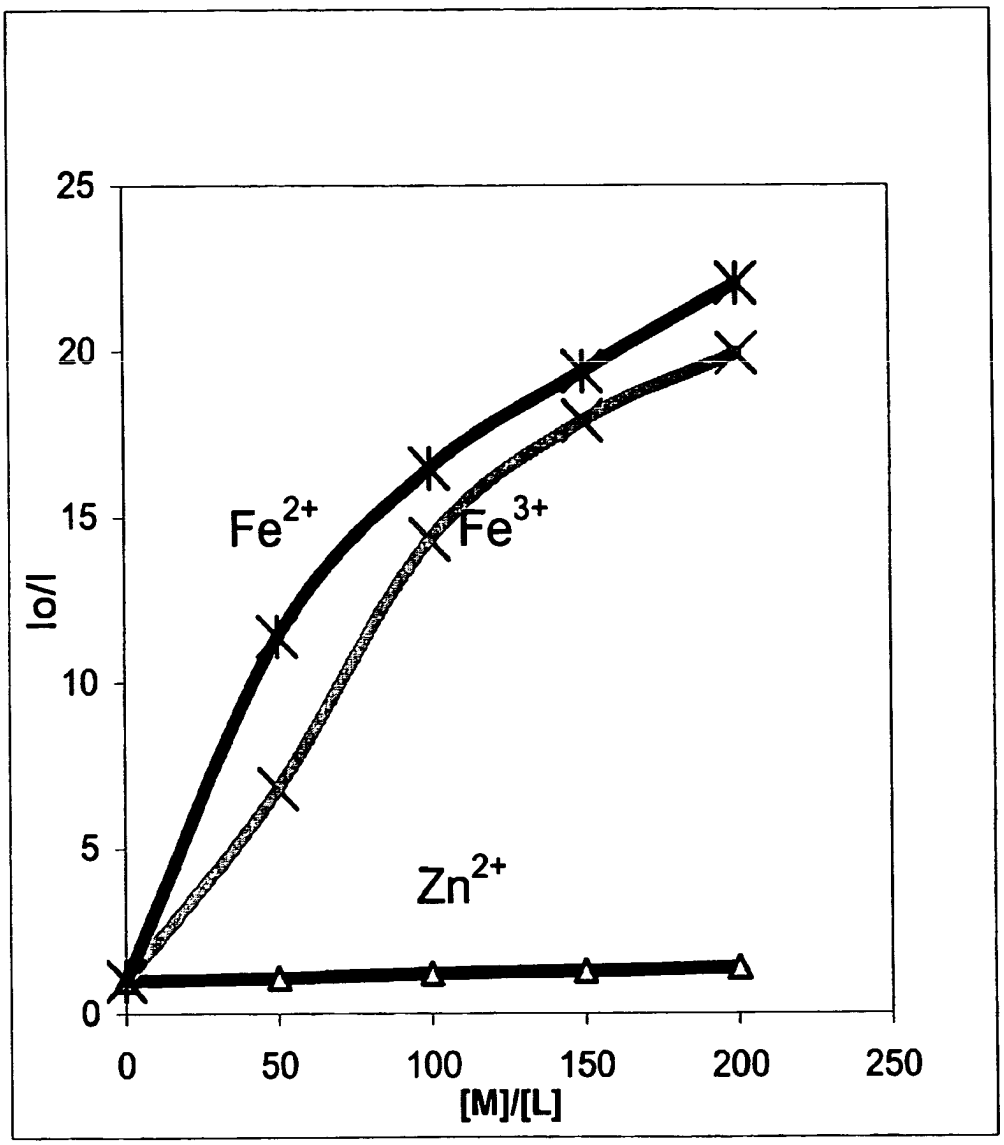


Figure 35

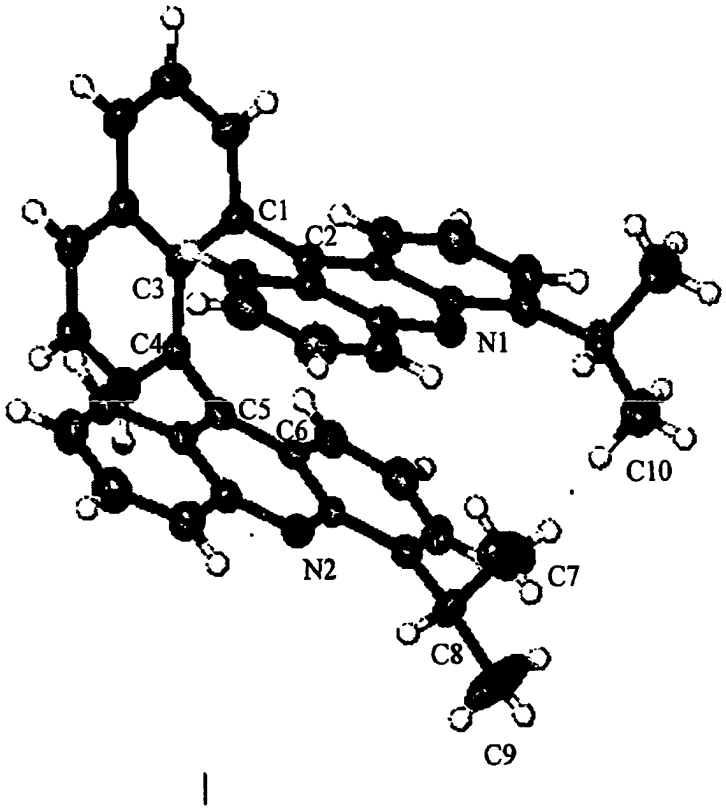


Figure 36

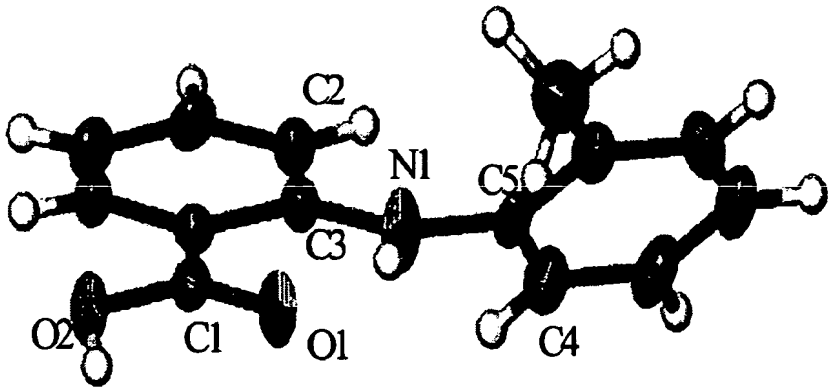
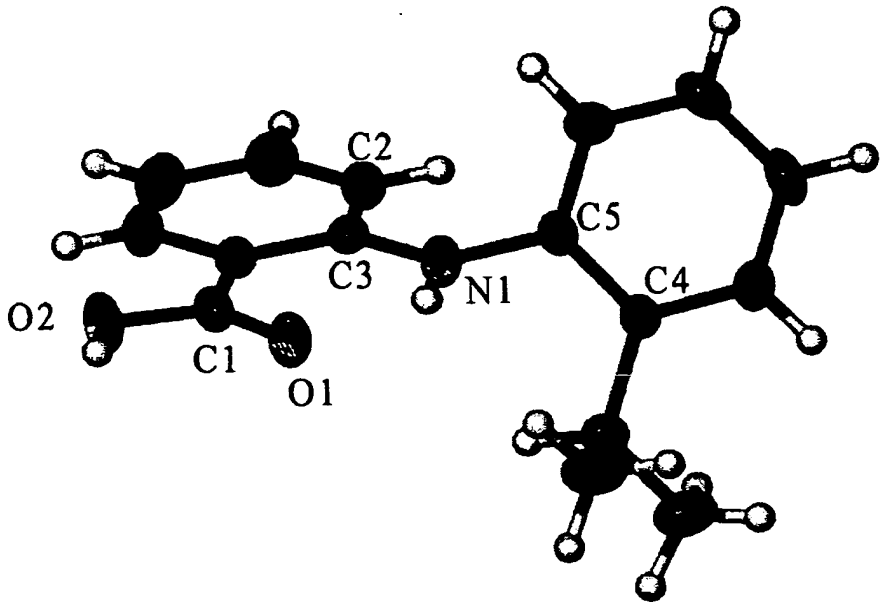


Figure 37



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Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse